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A CLINICAL AND RADIOLOGICAL CORRELATION OF THE LESIONS PRODUCED BY CHEMOPALLIDECTOMY AND THALAMECTOMY*

BY

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From the St. Barnabas Hospital for Chronic Diseases, New York

The purpose of this paper is to present the clinical and radiological correlation of 360 intracerebral lesions placed in 300 patients who underwent surgery for the treatment of Parkinson's disease. These cases represent a consecutive series of patients, part of a total of more than 800 basal ganglia operations performed on our service since 1952. Details of the surgical technique employed have already been reported (St. Barnabas Symposium on "Surgical Therapy of Extrapyramidal Disorders", 1956; Cooper, 1956; Cooper and Bravo, 1958a).

The cases selected for this study have been those operated on by using the balloon cannula technique (Bravo and Cooper, 1957) which allows testing of the physiological effects of a temporary lesion before the injection of alcohol and, by creating a small cavity, facilitates the production of a well-circumscribed alcohol lesion (Cooper and Bravo, 1958b). Such lesions, when the alcohol has been mixed with pantopaque, can be visualized radiographically.

In an earlier report we presented the anatomical evidence and the corresponding radiological landmarks obtained as a result of a study carried out in 65 cadaver brains (Bravo and Cooper, 1958). In that report we studied the anatomical location of 120 intracerebral lesions visualized radiographically and confirmed by anatomical studies of each brain. The conclusions of that paper regarding the radiological and anatomical correlations of certain lesions have been confirmed by other investigators (Amador, personal communication). The results of our anatomical study are also in essential agreement with the data that can be obtained from some of the available brain atlases (Stelmasiak, 1956; Spiegel and Wycis, 1952).

The surgical target in the present series of patients was the globus pallidus and/or the thalamus. In our anatomical studies we were also concerned with the radiological projection of these structures and estimation of limits of safety according to shape and size of the skull, size of the ventricles, and relative position of the foramen of Monro and pineal gland. As a result of continuing investigations a series of intracerebral structures have been radiographically outlined (Figs. 1 and 2) and the landmarks for the two surgical targets, namely the mesial globus pallidus and ventrolateral thalamus, were established (Cooper, Bravo, Riklan, Davidson, and Gorek, 1958). The results of the earlier studies can now be related to radiographically visualized lesions in patients.

In this paper we are going to consider the radiological location of these lesions in terms of the neurological results which they produced. With the information obtained from the cadaver study it is possible to correlate, with a fair degree of accuracy, the anatomical site of these lesions with the observed effects. However, until definite anatomical proof of the structures involved can be shown, when and if the brains of those patients come to post-mortem examination, we should limit ourselves to an evaluation of the clinical and radiological data.

Material and Methods

Three hundred consecutive patients, all of whom have been operated on by the balloon-cannula alcohol method, are included in this report. The follow-up period ranges from six to 18 months. We have excluded four patients who died in the immediate post-operative period as a result of intracerebral haemorrhage.

Altogether 360 lesions have been plotted in several standard *x*-ray tracings of the skull. For the dimensions of that skull and for the placement of the foramen of Monro and the pineal gland within it we have used a model made with a geometrical mean of the radiographs of all the patients considered. The lesions have been placed in those maps according to their relative position, in terms of the "foramen-pineal line" and in terms of the base line of the skull. The reason why we have chosen

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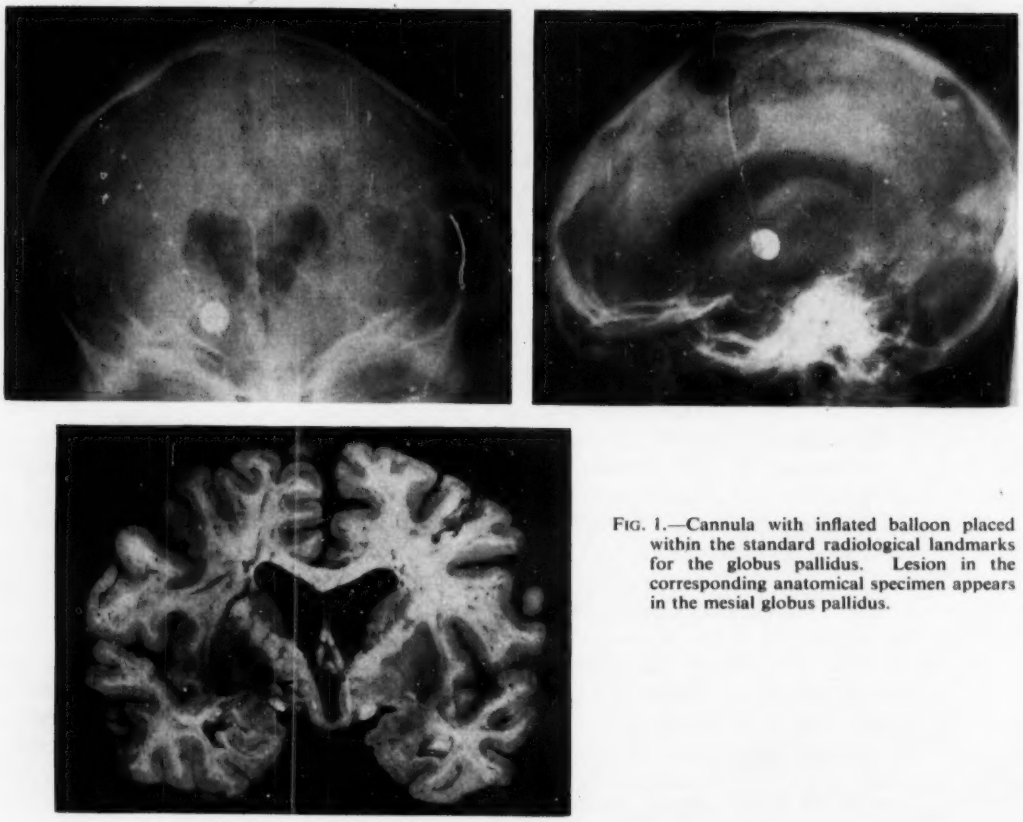

FIG. 1.—Cannula with inflated balloon placed within the standard radiological landmarks for the globus pallidus. Lesion in the corresponding anatomical specimen appears in the mesial globus pallidus.

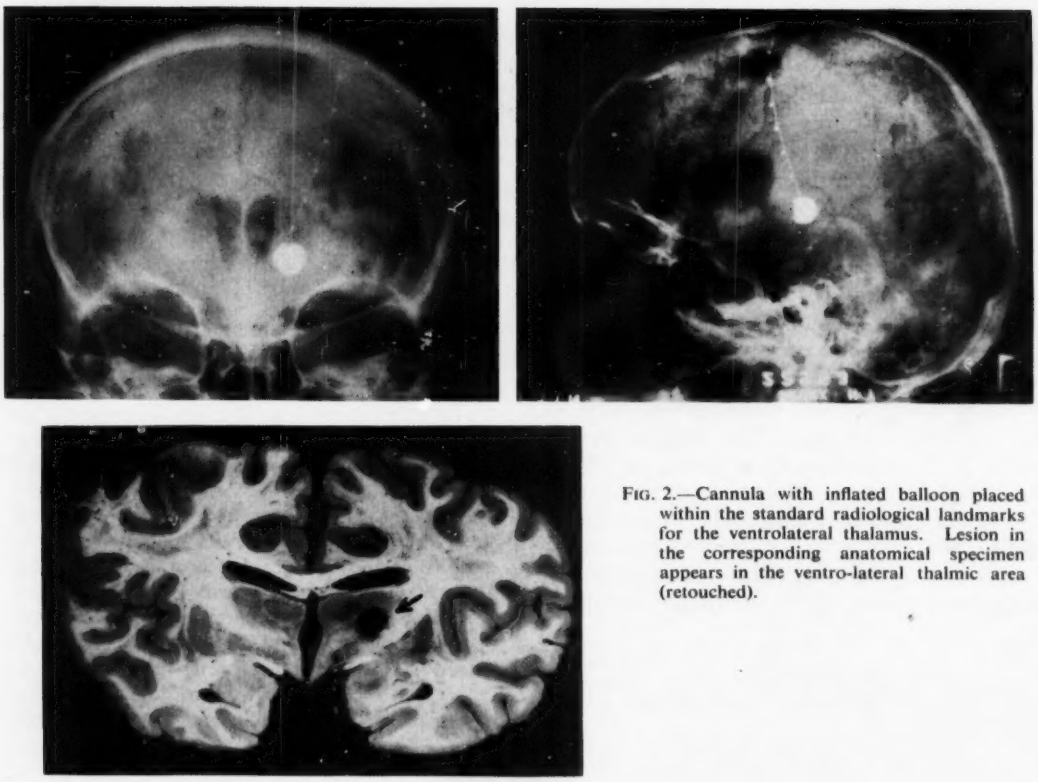

FIG. 2.—Cannula with inflated balloon placed within the standard radiological landmarks for the ventrolateral thalamus. Lesion in the corresponding anatomical specimen appears in the ventro-lateral thalmic area (retouched).

these reference points, and why we think that relative measurements in relation to them are valid, have been reported elsewhere (Bravo and Cooper, 1958). New data which consider the geometrical positions of the foramen of Monro and the pineal gland as related to the bony structures and relative dimensions of the skull will be the object of a later report.

In order to simplify the presentation, we have chosen as our reference point for the charts the geometrically central area of the lesion, although in some cases the actual lesion extended beyond the boundaries of the circles represented in the accompanying charts. Each point in the charts represents a minimum of three patients with some points corresponding to as many as 43 patients.

It is evident that, as had been intended at the time of surgery, the lesions fall into two main groups: those directed at the globus pallidus and efferent pallidal pathways, and those aimed at the ventrolateral area of the thalamus. In addition, it became evident that there were several points which showed a fairly constant radiological and clinical correlation outside of the standard limits of the surgical targets. In certain cases, lesions in these adjacent areas produced undesirable results; in other cases, temporary neurological effects with or without accompanying relief of tremor and rigidity were observed.

Results

The findings of this study have been summarized in five charts. Fig. 5 includes those lesions which affect primarily the globus pallidus and/or its efferent fibres. Fig. 6 includes those lesions which involve different areas of the thalamus and/or efferent or afferent thalamic tracts. We have summarized in Fig. 7 those areas from which serious undesirable effects were obtained. It should be noted that some of those points are based on a very small number of cases and that the complications were, with rare exceptions, temporary. But because of the constant and close relationship between each of those points and the corresponding clinical side-effect, it was considered worthwhile to call attention to it. In Fig. 8 we have isolated the distribution of those lesions causing motor weakness or sensory changes. In some instances the motor weakness was a transitory phenomenon observed in the operating room after inflating the balloon or inserting the cannula. Quick recovery followed the deflation of the balloon or the withdrawal of the cannula and most of these patients were successfully operated on at a later date. In only two instances the lesion thus produced left a residual motor deficit.

Two facts should also be mentioned in relation to the occasional motor deficit associated with chemopallidectomy or chemothalamectomy. (1) The lesion produced by the insertion of the needle or by inflating the balloon, even if incorrectly located, affects only a very small segment of the internal capsule and consequently only transient and temporary effects should be expected to occur (Fig. 3). (2) When the inflated balloon itself does not produce a motor deficit, it has never resulted in our experience from subsequent injections of alcohol into the same area unless some bleeding occurred. The explanation for this apparently lies in the fact that when the alcohol is deposited in the most lateral area of the thalamus, the thick fibre layers of the capsule at that level constitute a natural barrier and the alcohol necrosis appears to occur medialward into the soft thalamic tissue (Fig. 4).

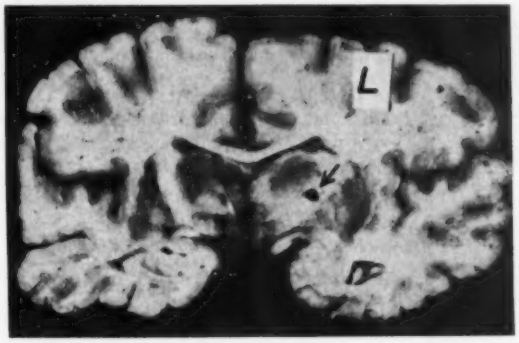

FIG. 3.—Lesion produced in the internal capsule by the inflated balloon.

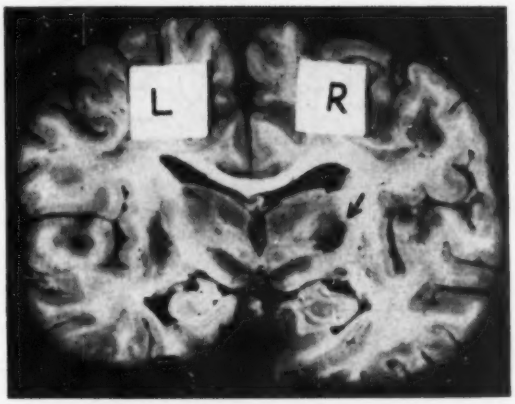

FIG. 4.—Lesion produced by the balloon plus injection of 0·5 ml. of alcohol into the ventrolateral thalamus. The lesion is sharply outlined against the internal capsule but it does not spread macroscopically among the fibres of the capsule.

Fig. 9 corresponds to the lesions in patient No. 297. This single patient summarizes some of the favourable and unfavourable effects produced by three different radiologically visualized lesions.

Pallidal Lesions.—The five different lesions represented in Fig. 5, which includes a total of 67 patients, correspond to the area of the globus pallidus and its efferent fibres. Although some other projection systems will also be involved with most of these lesions, we have to assume, at the present time, that

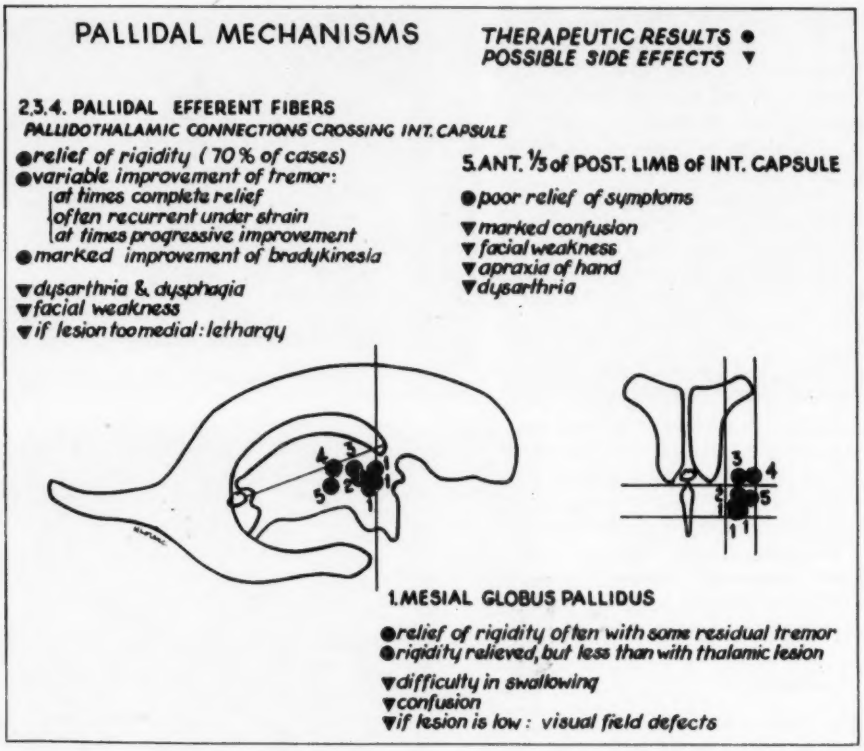
PALLIDAL MECHANISMS
THERAPEUTIC RESULTS ●
POSSIBLE SIDE EFFECTS ▼
2.3.4. PALLIDAL EFFERENT FIBERS
PALLIDOTHALAMIC CONNECTIONS CROSSING INT. CAPSULE
●relief of rigidity (70% of cases)
●variable improvement of tremor:
at times complete relief
often recurrent under strain
at times progressive improvement
●marked improvement of bradykinesia
▼dysarthria & dysphagia
▼facial weakness
▼if lesion too medial: lethargy
5. ANT. 1/3 of POST. LIMB of INT. CAPSULE
●poor relief of symptoms
▼marked confusion
▼facial weakness
▼apraxia of hand
▼dysarthria
1. MESIAL GLOBUS PALLIDUS
●relief of rigidity often with some residual tremor
●rigidity relieved, but less than with thalamic lesion
▼difficulty in swallowing
▼confusion
▼if lesion is low: visual field defects

FIG. 5

the effectiveness of these lesions in relieving Parkinsonian symptoms is due to destruction involving the globus pallidus and its efferent fibres, particularly the ansa and fasciculus lenticularis. Lesion No. 1 corresponds to the mesial part of the globus pallidus and it may extend from 10 to 18 mm. from the midline in the antero-posterior radiological projection (Fig. 1). In the lateral view, this lesion may extend from the level of the anterior commissure or anterior border of the foramen of Monro to 4 or 5 mm. behind the posterior margin of the foramen. It should be remembered that as we move posteriorly, part I of the globus pallidus moves away from the midline, so that the mesial globus is not in the same sagittal plane at the level of the anterior commissure, that it is 3 mm. behind the posterior margin of the foramen, but at both levels a pure pallidal lesion can be produced.

Lesion No. 1 has most commonly resulted in alleviation of rigidity and incomplete alleviation of tremor. Occasionally, complete relief of tremor is obtained. No ill effects follow this lesion. Lesion No. 2 affects the innermost part of globus I and the ansa lenticularis. It is possible, also, that some of the anterior fibres of the fasciculus lenticularis might be involved. Lesion No. 2 has generally resulted in a more complete relief of rigidity than lesion No. 1 and the relief of tremor is more often complete or almost complete. Regarding the relief of tremor obtained by this type of lesion, two additional points should be mentioned: (1) In some instances the relieved tremor would transiently reappear under strain. (2) In five cases, in which the rigidity was relieved but with marked residual tremor, we observed a gradual, progressive disappearance of the tremor, so that at the end of three months the patients were free of symptoms. Lesion No. 3 involves the antero-ventral segment of the thalamus and the fibres of the fasciculus and ansa as they run into it. This type of lesion has been followed by essentially the same results as lesion No. 2. Lesions Nos. 4 and 5 have in common the involvement of the anterior third of the posterior limb of the internal capsule, through which the fibres of the fasciculus project from the globus to the thalamus. At that level the internal capsule carries fronto-pontine and fronto-bulbar fibres and the anterior segment of the cortico-spinal pyramidal tract. Lesion No. 4, probably because of the involvement of the fasciculus lenticularis, had resulted in improvement of the Parkinsonian symptoms. The results in the cases with the lesion in area No. 5 have been consistently poor, and both lesions Nos. 4 and 5 have been followed on occasion by transient dysphagia, dysarthria, and facial weakness. When a lesion of this type is placed bilaterally lasting dysphagia and

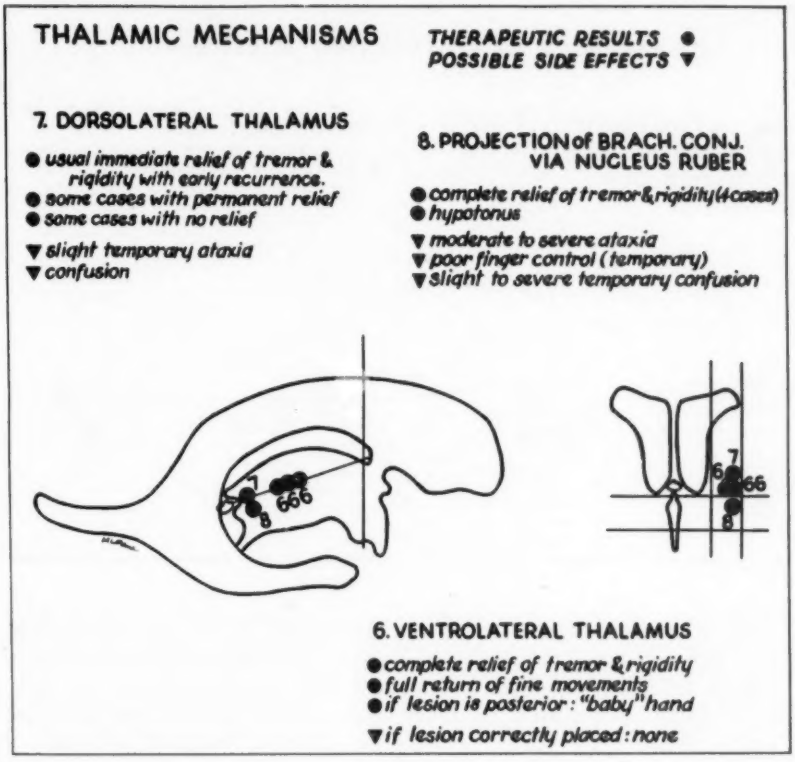
THALAMIC MECHANISMS
THERAPEUTIC RESULTS ●
POSSIBLE SIDE EFFECTS ▼
7. DORSOLATERAL THALAMUS
● usual immediate relief of tremor & rigidity with early recurrence.
● some cases with permanent relief
● some cases with no relief
▼ slight temporary ataxia
▼ confusion
8. PROJECTION of BRACH. CONJ. VIA NUCLEUS RUBER
● complete relief of tremor & rigidity (4 cases)
● hypotonus
▼ moderate to severe ataxia
▼ poor finger control (temporary)
▼ slight to severe temporary confusion
6. VENTROLATERAL THALAMUS
● complete relief of tremor & rigidity
● full return of fine movements
● if lesion is posterior: "baby" hand
▼ if lesion correctly placed: none

FIG. 6

dysarthria may occur. The only other undesirable effects of this group of pallidal lesions have been drowsiness and apathy of a temporary nature.

It should be noted that division within these areas, all of them included within little more than a cubic centimetre of brain, is somewhat artificial. We are speaking in terms of main localization of the lesion and of predominant symptoms. Some small lesions have reproduced rather sharply the effects attributed to a certain localized area; larger destruction, on the other hand, will extend beyond the boundaries of one specific area and the combined effects of lesions in two or three of the described structures would follow.

Thalamic Lesions.—In Fig. 6 we have represented those lesions, 183 in all, which we believe correspond to the ventrolateral region of the thalamus posterior to the anteroventral nucleus. Area No. 6 includes three points, all within the ventrolateral thalamus from which constant results regarding the relief of tremor and rigidity have been obtained. This area seems to start at a point midway between the foramen of Monro and the pineal gland and to extend backwards to a point 7 to 8 mm. in front of the pineal gland. In the antero-posterior projection of the radiograph the centre of the area occupies a point 14 to 20 mm. lateral to the midline (Fig. 2). Details as to the possible structures involved in this type of lesion have been given in a previous anatomical paper. It is not clear at this time if the small variations in the radiological location of that point from which specific response regarding relief of tremor and rigidity can be obtained are due to differences in the radiological projection of the thalamus (due, in turn, to anatomical variations in that particular brain) or if they are related to differences from case to case regarding the physiological mechanisms responsible for the tremor and the rigidity.

Lesions within this area, No. 6, especially in its posterior part, have resulted in relief of tremor and rigidity in practically every case. It should also be noted that we have observed with this type of lesion a return of the fine voluntary movements of the fingers, usually within a period of minutes after placing the lesion. Lesions confined to the limits of area No. 6 have not resulted in any ill effects. In several cases we have observed a certain spatial arrangement within this area, in such a way that following insertion of the needle the relief of the leg symptoms would be obtained from a point postero-caudal in relation to that point affective for the relief of the arm symptoms.

Area No. 7 occupies a zone immediately dorsal and posterior to that of area No. 6. Anatomically, it

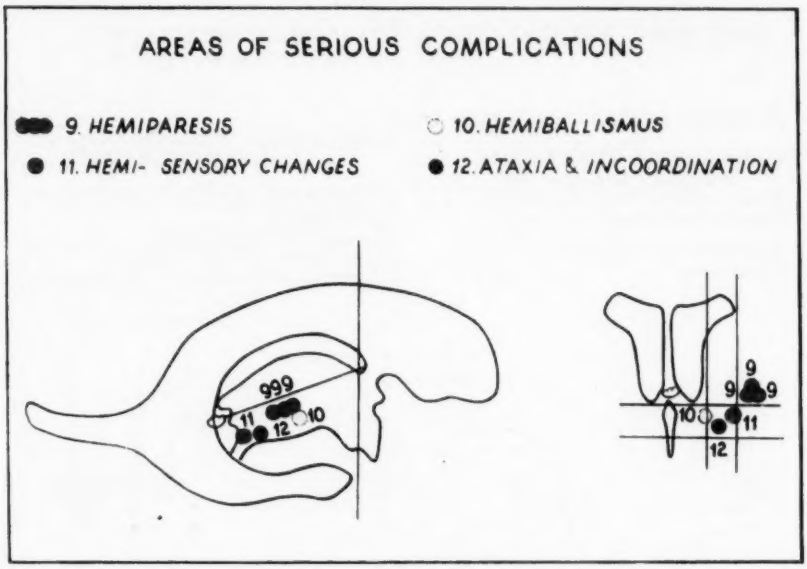

FIG. 7

seems to represent a different zone of the thalamus and, according to our own anatomical studies, areas Nos. 6 and 7 affect different structures and cannot be in the same thalamic nuclei, even if one takes into account the widest possible margin of radiological and anatomical variations. Since the results in some cases with lesions at the level of area No. 7 have been very similar to those obtained at area No. 6, it must be assumed that either two different areas can respond in a similar manner, or that we are interrupting the same pathway at two different levels. This also applies, with certain limitations, to point No. 8, discussed below, and if the concept is widened it would similarly include the favourable pallidal lesions.

Area No. 8 seems to involve the posterior segment of the most ventral part of the lateral thalamus, which receives fibres from Forels fields and, in part, the post-rubral radiation of the brachium conjuntium. Lesions in this area have been followed by relief of tremor and rigidity with a good return of fine voluntary motion, accompanied by a variable degree of temporary incoordination of the limbs, which is manifested by past-pointing, swaying of the raised limb, and a certain clumsiness in manipulation. These signs, minimal in most instances, have cleared within a period of three weeks with maintained relief of tremor and rigidity. Usually, these "cerebellar" signs have been more marked in the medial part of area No. 8. It is possible that the lowermost segment or area No. 8 may also involve projections to or from the substantia nigra.

The thalamic lesions at the indicated points have consistently resulted in an immediate and complete relief of tremor and rigidity. Except for the occurrence of temporary incoordination at point No. 8, no ill effect seems to result from these lesions. A complete looseness or hypotonicity of the affected limbs, without weakness and with full range of voluntary motion, can be observed within seconds or minutes after inflating the balloon in these sites. It should be noted, however, that the exact point of specific response seems to vary a few millimetres from patient to patient, and that careful, persistent testing is necessary before considering a placement as final.

Areas of Serious Complications.—Points marked 9 in Fig. 7 are based on the radiographs of seven patients who developed weakness of the contralateral extremities when the needle reached that particular level or when the balloon was inflated in that region. The motor impairment varied from a weakness of grip and heaviness of the arm and leg to a complete flaccid paralysis. All of these patients but one recovered within a period of two to four weeks. In four of the cases, recovery has been complete. Two show residual signs, namely, increased deep tendon reflexes, slight weakness of the hand, and some limitation in the fine movements of the fingers. The remaining patient still has a moderate hemiparesis nine months after surgery. Every one of these patients developed an immediate contralateral sign of Babinski and three of them with lesions in the dominant hemisphere had language difficulties which followed the same favourable evolution as the hemiparesis. It is to be noted that these patients with presumably localized capsular lesions remained

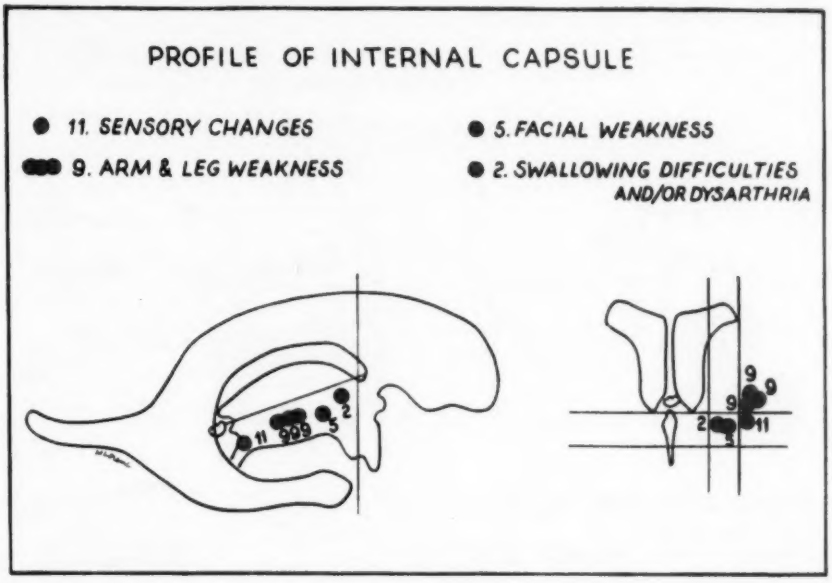
PROFILE OF INTERNAL CAPSULE
11. SENSORY CHANGES
9. ARM & LEG WEAKNESS
5. FACIAL WEAKNESS
2. SWALLOWING DIFFICULTIES AND/OR DYSARTHRIA

FIG. 8

alert and fully conscious in contrast to those patients who developed motor deficits as a result of intracerebral haemorrhage.

This area 9 is immediately lateral to area 6 in our charts. The internal capsule curves at that level around the lateral and caudal aspects of the thalamus. According to our clinical experience, the motor fibres, the lesion of which would cause a hemiparesis, are concentrated in a narrow band behind the mid-point in the foramen-pineal line.

There have been two additional cases in which a hemiparesis was produced on the operating table. These two patients had had previous surgery at the level of point 4, that is, involving the pallido-fugal fibres and the anterior third of the posterior limb of the internal capsule. No motor deficit resulted at that time, but the symptoms (Parkinsonian tremor and rigidity in one case, and dystonia musculorum deformans in the other) eventually recurred. The patients were operated on again and in both cases the needle entered area No. 9. The hemiparesis which resulted was not of the flaccid type. On the contrary, spasticity developed within a matter of minutes. The hand of the patient could be seen closing and acquiring the posture of a long-standing hemiparetic limb. Both patients improved a great deal with the passing of time, but residual spasticity remained. Whether this phenomenon was due to a double lesion affecting pyramidal and parapyramidal fibres remains open to speculation.

Point No. 11 of this chart represents that area from which sensory abnormalities have been observed. The changes have been in the form of a hypaesthesia and hypalgesia affecting light touch, pin prick, temperature, and pain threshold as measured by galvanic stimulation. These sensory changes have been observed in a total of eight cases. In two of them they were in the form of a hypaesthesia and hypalgesia affecting subjectively the entire contralateral half of the body. Objectively, the sensory changes were more marked on the face and distal part of the extremities. One of these patients has not been available for follow-up examination. The other patient, one year after surgery, still has subjective hemisensory changes, but on objective examinations only patchy areas of hypaesthesia and hypalgesia could be observed on the affected side of the body. The remaining five patients had sensory changes of a similar nature, but limited to the perioral area and to the index finger in one case, and the tips of the second, third, and fourth fingers in the remaining four patients. These changes subsided subjectively and objectively in a period of one to three weeks following surgery.

There have been no cases in which position or vibration senses have been affected.

Lesions at the level of point 10 have resulted in contralateral involuntary movements in 11 patients. These movements are difficult to describe as a clinical entity and in some cases resemble hemiballistic movements, and in other cases they took the form of a choreoathetosis. The hand alone was involved in five cases, the arm and the leg in three cases, and the entire contralateral side of the body in three cases. Those cases with movements limited to the hand cleared spontaneously in a maximum of two weeks. Those cases with movements in the arm and leg cleared spontaneously between one to three

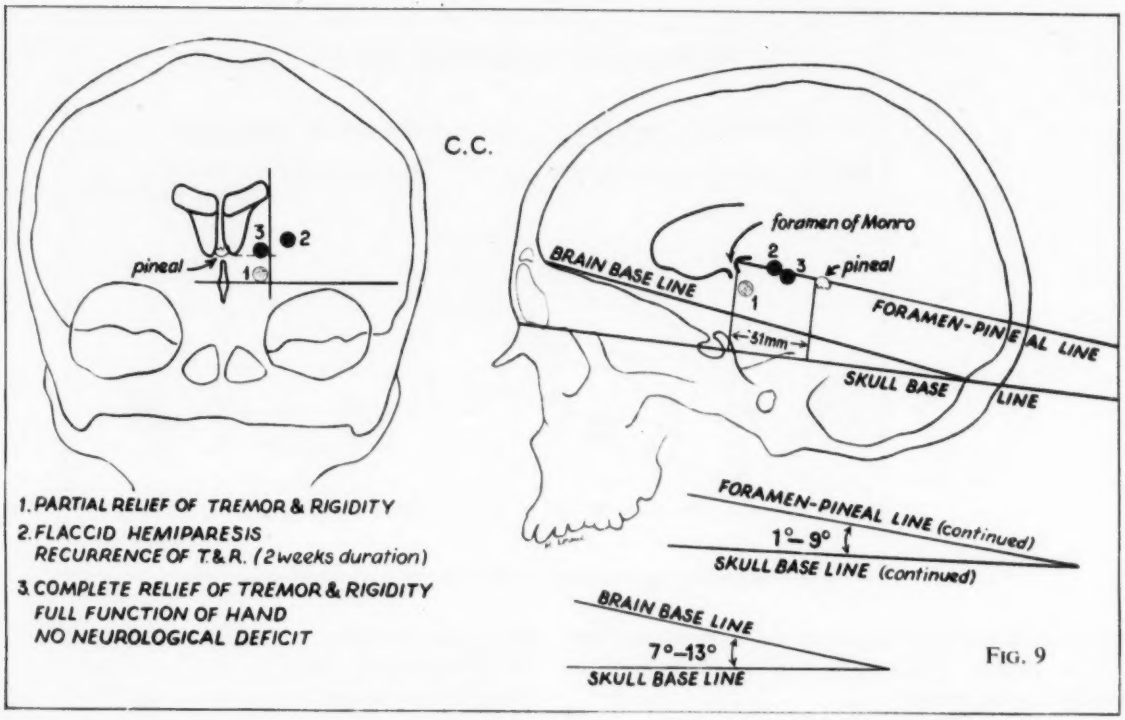

FIG. 9

weeks following the onset. Every one of these eight cases eventually had a complete relief of tremor and rigidity in the involved extremities.

Of the three cases with severe choreoathetosis, two of them occurred following bilateral operations, and one of them after a unilateral operation. One of the bilateral cases cleared totally after two weeks of severe choreoathetosis and resulted in complete relief of tremor, rigidity, and bradykinesia. The second of the bilateral cases had mild involuntary movements at the time of discharge from the hospital six weeks after surgery. One patient in this group developed a severe contralateral hemiballismus a few hours after surgery. The involuntary movements slowly subsided and had virtually disappeared within four months at which time the patient died as a result of a carcinoma of the head of the pancreas. Post-mortem examination of the brain revealed a small lesion affecting the fields of Forel and the lateral half of the subthalamic nucleus of Luys. This is probably the same area involved in the other patients with lesions at point 10. Radiologically, point 10 appears at a level 5 to 9 mm. below the middle third of the foramen-pineal line and 4 to 10 mm. from the midline.

This series of cases of surgically induced involuntary movements will be the object of a detailed report at a later date.

Point No. 12 in Fig 7 represents a region in which surgery has resulted in ataxia, incoordination, and marked hypotonus. These effects are not really serious complications. There has been a gradual recovery in every case and the initially ataxic, hypotonic side has returned to normal function with a maintained relief of the tremor and rigidity.

In Fig. 8 we have summarized some of the points of the previous charts, those from which motor or sensory deficits have been produced, thus giving a radiological and clinical outline of the distribution of the fibres of the internal capsule. Basically this outline is in agreement with the known distribution of anatomical fibres. We have, however, found that those lesions that seem to be responsible for contralateral weakness of the limbs are distributed more posteriorly than one would expect from the standard descriptions in anatomical textbooks. That is, those fibres carrying motor impulses to the contralateral extremities are affected only by lesions at least 15 mm. behind the foramen of Monro at the level of the foramen-pineal line, well behind the so-called genu of the capsule. The question of level of depth of the lesion is important when one considers the distribution of fibres in a sagittal plane because of the double curvature in the internal capsule. This curvature is such that the so-called genu of the capsule becomes displaced posteriorly as the fibres run downward.

As can be seen in Fig. 8, facial weakness has been

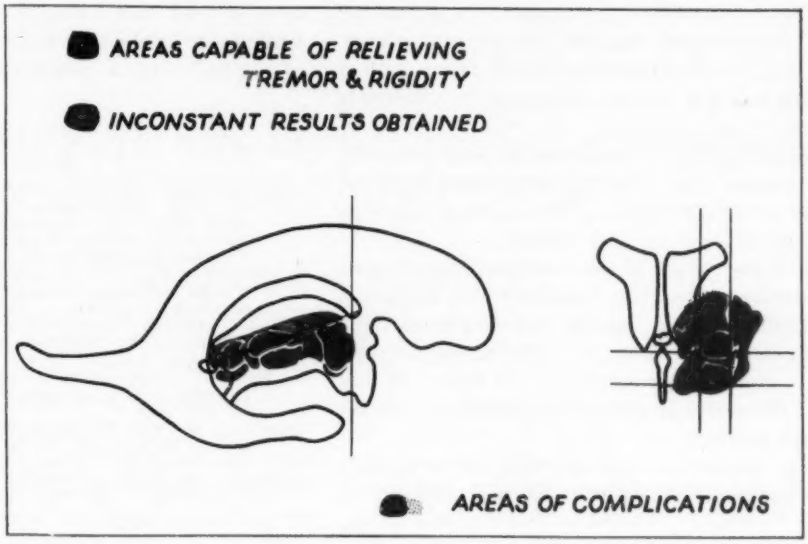

FIG. 10

obtained from the anterior segment of the posterior limb of the capsule. When a more posterior segment of the capsule is affected by a lesion the arm will show more marked deficit than the leg without evidence of a specific distribution of fibres. This is the same phenomenon clinically observed after cerebral vascular accidents.

A similar finding of greater susceptibility of the hand and facial fibres have been found at point 11 from which sensory changes were obtained. In most instances the face and the hand, especially the index and middle fingers, showed the more pronounced subjective and objective sensory deficits irrelevant of the special point of lesion.

Fig. 9 emphasizes some of the points of Fig. 6 in relation to the clinical evolution of case No. 297, Mrs. C. C. This 61-year-old woman with Parkinsonism manifested primarily by tremor and rigidity in the right extremities underwent a left transfrontal chemopallidectomy with placing of a well localized lesion at point No. 1 of Fig. 9. Complete relief of rigidity with recurrence of the tremor 10 days after surgery resulted. There were no neurological deficits. Re-operation was decided upon, and the needle was inserted and the balloon inflated at point No. 2 of Fig. 9. Immediately right flaccid paralysis and motor aphasia resulted. The balloon was at once deflated and the needle withdrawn. Progressive recovery of the motor symptoms and aphasis followed and at the end of two weeks the patient was in the same state as before her second operation, tremor included. The third operation was carried out four weeks later. This time the lesion was successfully placed at point No. 3 of Fig. 9 with immediate relief of the tremor and no signs of neurological deficits. This patient has been followed for over one year and has remained free of tremor and rigidity in the right extremities with normal function of the hand and no signs of involvement of the pyramidal tract.*

Fig. 10 is a composite drawing of the favourable, unfavourable, and "neutral" lesions as they appear in the radiographs. Areas from which good clinical results have been obtained without neurological ill-effects are represented in green. Lesions which have resulted in neurological complications are represented in red. And finally, those "in-between" areas where results have been inconstant or temporary and the side-effects, for the most part, negligible, are represented in blue.

Two things should be emphasized: first that there is no sharp limit between the green and blue areas, although there seems to be a narrow margin of safety between blue or green and red areas, especially at posterior-external and posterior-inferior levels. Second, that we are dealing with tri-dimensional structures that are represented here in two dimensions, and consequently, there is a superimposition of areas which cannot be shown in the figures. For the representation, preference has been given to the red in both antero-posterior and lateral projections; any lesion which falls within a red area either in the antero-posterior or in the lateral view is likely to be without clinical benefit and result in a neurological complication.

Conclusions

The most constant and complete relief of both alternating tremor and rigidity is obtained from a

*Since this paper was submitted the same patient has been successfully operated on for her other side.

lesion in the region of the ventrolateral nucleus of the thalamus. No abnormal sensory, motor, intellectual, or psychological abnormalities result from such a lesion. This lesion is the one of choice for treatment of both tremor and rigidity.

Involvement of cerebellar pathways to the ventrolateral thalamus undoubtedly contributes in some measure to the effectiveness of this lesion in alleviating Parkinsonian tremor and rigidity.

Lesions of the mesial globus pallidus, the efferent pallidal pathways, and the antero-ventral thalamus provide good relief of rigidity but less consistent relief of tremor. However, in some cases, tremor, which was incompletely relieved by a lesion in this complex, will gradually disappear completely within two or three months.

The areas responsible for neurological complications are distributed in a predictable manner, in such a way that those complications can be prevented—or when they occur be explained—in terms of the radiological placing of the lesion.

References

Bravo, G., and Cooper, I. S. (1957). *J. Amer. Geriat. Soc.*, **5**, 651.

——, ——(1958). *Anatomical and Radiological Correlations in Relation to the Placement of Therapeutic Lesions into the Basal Ganglia.* Presented at the New York University Symposium on extrapyramidal disorders on May 15, 1958. To be published.

Cooper, I. S. (1956). *The Neurosurgical Alleviation of Parkinsonism.* Charles C. Thomas, Springfield, Illinois.

——, and Bravo, G. (1958a). *J. Neurosurg.*, **15**, 244.

——, —— (1958b). *Neurology*, **8**, 344.

——, ——, Riklan, M., Davidson, N. W., and Gorek, E. A. (1958). *Geriatrics*, **13**, 127.

St. Barnabas Symposium on Surgical Therapy of Extrapyramidal Disorders (1956). *J. Amer. Geriat. Soc.*, Vol. IV, Number 12, pp. 1171-1319.

Spiegel, E. A., and Wycis, H. T. (1952). *Stereoencephalotomy.* Part I: *Methods and Stereotaxic Atlas of the Human Brain.* Grune and Stratton, New York.

Stelmasiak, M. (1956). *Anatomical Atlas of the Human Brain and Spinal Cord.* Polish State Medical Publishers, Warsaw.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 11.

SOME ASPECTS OF THE EFFECTS OF ACUTE RESERPINE TREATMENT ON BEHAVIOUR

BY

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Hitherto behavioural investigations with reserpine have been confined to the use of very small doses, doses which weight for weight are considerably lower than those used in clinical work. Sidman (1956) used a Skinner lever pressing apparatus for investigating the effect of up to 0·1 mg./kg. reserpine on work under different reinforcement programmes. Smith, Wagman, Wagman and Riopelle (1956), investigating the effects of reserpine on conditioned avoidance behaviour in monkeys with brain lesions, used doses between 0·15 and 0·37 mg./kg. However, pharmacologists have reported interesting effects with more substantial doses in a variety of species. In particular, attention can be drawn to the atypical sedation induced by the drug. Unlike other depressants of the central nervous system, *e.g.*, barbiturates, reserpine produces no anaesthesia, as animals can always be roused by external stimulation. Further, a paradoxical behaviour and electro-encephalographic pattern appears. Rats, for example, appear chronically sedated to the observer but have an alerted E.E.G. At the same time the limbs of drugged rats can be positioned in catatonic-like postures, deep body temperature falls steeply, and the sympathetic division of the autonomic nervous system appears to be blockaded.

Subsequent reports will deal with experiments designed to determine the connexion between the pharmacological and physiological properties of the drug and behaviour. The present paper is concerned with accounts of the drug concentrations and the time factors which are involved in a behavioural disturbance induced with reserpine. In order to accomplish this it was necessary to discover the course of the reserpine disturbance in the rat—the onset, the duration, and the time of recovery—by employing some behavioural criterion. For this purpose two measures were employed, response latency, that is, the time taken by the rat from the moment of entry into the apparatus to when it began to run, and a locomotor time score obtained from a straight runway apparatus. It was held that latency could be taken as the time required for the rat to organize its response in a given situation. In view of the known high specificity of reserpine treatment on the central nervous system it was postulated that this measure would be adequately sensitive. Locomotor efficiency was tested by measuring the time taken by the rat to move over a fixed distance. A 100 decibel mixed frequency noise generator was used to induce running behaviour in the apparatus after a criterion latency time had been exceeded.

Design

A concomitant variation design was used for this experiment. The work was spread out over three weeks, with the middle week as a control period, in order to ensure that there would be no carry-over effect in the treatment in the first week to the third week. The design is set out in Table I. The behavioural measures employed were latency of response and running time. The two controls were, first, the vehicle in which the reserpine raw material was dissolved,* and secondly, an equal volume of distilled pyrogen-free water. Owing to the long delay found in the drug's onset, and the relatively large number of animals treated, it was decided to test the drug's activity every quarter of an hour after injection. The number of test-hours was limited to five. Pilot runs with scrub animals showed that recovery could not be expected for from 24 to 36 hours. On the morning after treatment, *i.e.*, 22 hours, rats were placed in the apparatus every hour and tested for recovery.

All animals were randomly assigned to a particular treatment. Litter mate controls were not considered. After each part of the experiment had been concluded all rats were again assigned at random for the new treatment and rested for seven days, although they were maintained on running schedules. One of the complex

*The reserpine raw material employed in the first week of the experiment was kindly supplied by CIBA Laboratories. The reserpine was made up in an appropriate injection vehicle.

The formula employed was:—

Reserpine	100 μg.
Ascorbic acid	4·56 mg.
Sodium bicarbonate	80 μg.
Distilled water to 1 ml.	

TABLE I
EXPERIMENTAL DESIGN

	Treatment Order	No. of Rats per Treatment	Dose	Measure
Week 1: Randomly assigned	Experimental Group I	5	6 µg./kg.	Latency and running time
	" Group II	5	25 " "	" " " "
	" Group III	5	50 " "	" " " "
	" Group IV	5	100 " "	" " " "
Week 2: Randomly assigned again	Control 1	10	1 ml. distilled water	" " " "
	" 2	10	1 ml. reserpine vehicle	" " " "
Week 3: Randomly assigned again	Experimental Group V	5	0·6 mg./kg.	" " " "
	" Group VI	5	1·25 " "	" " " "
	" Group VII	5	2·5 " "	" " " "
	" Group VIII	5	5 " "	" " " "

problems which bedevils this type of study is to select the correct, *i.e.*, suitable for the experimental requirements, range of drug dosage levels. If one considers the intensity of the effect of the drug as being related to its concentration in the body, then the intensity may vary from the imperceptible to one which is so severe as to be useless. Hence 10 mg./kg. of reserpine, while not fatal, produces symptoms of such apparent severity that the rat, which is violently ill for several days, is useless for the continuation of the experiment. The range of drug concentrations was selected so that in the first experimental trials the dosages were worked up in geometric progression, from a dose level known from the pilot work to be ineffective. In the second experimental trials the dosages were worked down in a geometric progression from a known high level, that is 10 mg./kg. This procedure permitted a most economic sampling along the drug dosage continuum. A noise generator was employed in order to test the susceptibility of drugged rats to auditory stimulation.

Subjects

The subjects of these experiments, 20 male albino rats obtained at weaning, were from the Medical Research Council Toxicology Unit, Carshalton, Surrey. The animals were uniformly handled and treated throughout the experiment. They were fed on the approved Medical Research Council diet 41B (Bruce and Parkes, 1949). At 80 days the rats were placed on a two-hour feeding schedule. Training in the apparatus started at the age of 100 days. Experimental and control injections were made intraperitoneally.

Procedure and Apparatus

Experiments were conducted in a 2½-metre runway under hunger motivation. All aspects of this procedure and the apparatus have already been described in detail (Glow, 1957).

The Effect of Reserpine on Behaviour

In the rat, reserpine produces a state of relative immobility associated with some degree of peripheral tremor. The rat's body is hunched tightly together, with the head sagging to the floor. The back legs are splayed out, probably in order to balance the body weight adequately (Fig. 1*a* and *b*). Using a drug dosage level of 5 mg./kg., it becomes possible to

FIG. 1*a*

FIG. 1*b*

FIG. 1*a*.—Splayed back legs in rat.

FIG. 1*b*.—Position of head when animal is placed on the floor.

FIG. 2*a*

FIG. 2*a*.—Atypical positions of limbs.

FIG. 2*b*.—Interlocking of hind paws in rat, and position of the head, when animal is held.

FIG. 2*b*

place and keep the rat's limbs in atypical positions (Fig. 2*a*). This positioning of the rat's limbs must be done slowly and gently so as not to constitute sufficient stimulation to arouse the animal. An adequate arousal stimulus will produce a righting reflex and typical body posture adjustment. The chronic ptosis seen with reserpine treatment is the first characteristic symptom to appear and the last to be extinguished, being present in varying degrees from 30 minutes after injection to 72 hours. For the first 18 hours reserpine-treated rats deprived of food showed no interest in it. After this period elapsed, rats almost attacked food, eating voraciously for a short period, and then generally relapsing back into the tranquillized state. A condition of increased appetite to the point of " true polyphagia " was also " universally " found in schizophrenics as a result of reserpine treatment (Tasher and Chermak, 1955).

The rat's condition is marked by the frequent spasmodic and jerky head and limb movements. These spastic, paralytic-like movements are found particularly in the region of the head and neck. The motor disturbance observed was never flaccid, as the limbs when moved by the experimenter offered a continuous resistance. The resistance to passive movement appears to be a function of the rate and degree with which the pressure is applied. Gentle placement produces less resistance than when the limb is pushed energetically. Muscle tone appears to be continuously high. Drugged rats, when placed on their backs have frequently assumed a foetal-like posture, instead of the usual righting reflex response. In these cases the animals have attempted to lock their front and hind paws together, while lying on their convex-shaped backs. An example of hind paw locking may be found in Fig. 2*b*. Reactions to tactile stimulation, *e.g.*, the vibrissae is negligible, as indeed are responses to what would normally be considered painful stimulation. The position in which the animal is held in Fig. 2*b* is tolerated for as long as the experimenter is prepared to hold the rat. Particularly noteworthy is the position of the head in this figure. When using ether or barbiturate sedation the head sags between the shoulders when the rat is held in this position.

The effect of auditory stimulation is difficult to assess. Rats make no attempt to move away from a source of noise of approximately 100 decibel mixed frequency, there being no head deflection. It was possible that the external pinnae moved to locate the source of the sound, but such movements were confused by the tremor and spasmodic jerking of the head. There was some tendency during the noise for the hyperkinetic symptoms to increase, the incidence falling off when the noise was switched off.

The effect of visual stimulation was difficult to evaluate. The eyes are generally completely shut by the drug's effect. A 100-watt light source brought close to the rat's eyes causes no head deflection. On the other hand rats appear to avail themselves of the light as a source of heat. One of the most remarkable features of this tranquillizing agent is the paradoxical aggression produced 24-36 hours after administration to the albino rat. If the rat is disturbed at this time it will indiscriminately and viciously attack the experimenter or any item introduced into the cage with a fury seldom seen

among normal tamed laboratory rats. This phase wears off quickly and the animal resumes its usual posture and tremor. This aggression can also be invoked by relatively light stimulation of, *e.g.*, the vibrassae. An interesting fact is that once such an aggression has taken place, it does not occur again even with quite painful stimulation.

Results

The results from this preliminary experiment fall into two kinds; those which compare the controls, and the effect of the drug, and those which are concerned with the differential effects of the drug on various treatment groups. In Table II is shown the mean scores of two groups of 10 rats. These constitute the two control groups. The table is comprised of 20 scores, progressively arranged, so that each score is a sample of the rat's behavioural capacity, taken at quarter-hour intervals from the time of injection.

By inspection it would appear that there is no difference in the effects of the two treatments. The animals rapidly settled down to a fairly steady level of performance, which was maintained for a number of hours. In all the observations given, it is difficult to use a convenient statistic to calculate possible significant differences between groups. This is due to the dependence that exists between successive observations on the same subject. In order to offset the statistical difficulty encountered, a test of significance between the total latency times of the animals in each group was undertaken. Using the t test for unrelated means, it was found that $t = 0{\cdot}0034$ with 18 degrees of freedom, which is insignificant at the 5% level.

In Table III may be found the mean times for all experimental groups. These results have been set

TABLE II

MEAN TIMES OF CONTROL GROUPS

Trial No.	Distilled Water Group		Reserpine Vehicle Group	
	Mean Latency	Mean Running Time	Mean Latency	Mean Running Time
1	4	2	9	6
2	6	2	7	7
3	5	3	5	6
4	7	3	6	6
5	6	4	6	3
6	5	3	4	3
7	6	4	5	3
8	6	2	5	3
9	3	3	3	2
10	3	3	3	3
11	3	2	4	3
12	3	2	3	2
13	4	2	3	2
14	3	2	3	3
15	3	2	4	3
16	4	2	3	2
17	5	4	4	2
18	3	3	3	2
19	3	2	4	5
20	3	2	3	2

All means were taken to the nearest whole number.

TABLE III

MEAN EXPERIMENTAL TIMES OF FIVE RATS IN EACH GROUP GIVEN RESERPINE

Trial No.	Week 1								Week 3							
	Group I (6 μg./kg.)		Group II (25 μg./kg.)		Group III (50 μg./kg.)		Group IV (100 μg./kg.)		Group V (0·625 mg./kg.)		Group VI (1·25 mg./kg.)		Group VII (2·5 mg./kg.)		Group VIII (5 mg./kg.)	
	Latency	Running Time	Latency	Running Time	Latency	Running Time	Latency	Running Time	Latency	Running Time	Latency	Running Time	Latency	Running Time	Latency	Running Time
1	2	4	3	5	3	4	6	10	3	3	5	7	2	11	6	4
2	4	3	6	3	3	5	5	3	4	3	3	2	2	6	5	3
3	7	3	3	2	6	2	7	4	2	3	4	3	2	6	5	4
4	3	3	9	2	6	6	3	2	3	2	5	3	3	10	4	3
5	3	3	4	2	3	9	3	7	3	3	3	3	12	8	2	3
6	5	3	3	2	2	4	3	4	2	4	3	4	7	14	3	4
7	3	6	2	3	7	2	9	3	4	3	107	58	78	29	121	87
8	5	4	2	2	10	11	15	9	4	7	312	119	258	96	370	121
9	4	4	8	2	14	9	11	12	12	8	Experiment terminated		Experiment terminated		Experiment terminated	
10	2	4	2	2	6	2	13	3	164	59						
11	9	3	9	13	8	7	7	10								
12	2	3	3	5	5	4	5	6	Experiment terminated							
13	5	7	3	4	4	4	8	6								
14	4	4	3	15	3	4	11	20								
15	3	4	5	2	3	2	5	4								
16	7	4	7	5	3	3	7	9								
17	3	5	4	2	3	6	12	7								
18	3	4	6	3	7	5	3	6								
19	4	3	3	2	3	4	7	8								
20	3	4	2	4	4	3	6	6								

All means were taken to the nearest whole number.

out in the same progressive order used in Table II. The cessation of running behaviour was obtained two hours after injection. At that trial the animals would not move either during the maximal five-minute latency, or during the succeeding two minutes with the noise generator switched on. In considering the latency times of the four high-dosage experimental groups, and comparing these with the performance of the reserpine vehicle controls in Table II, it is apparent that the behaviour changes can be safely attributed to the effects of reserpine.

It was thought instructive to examine the data from the experimental groups and test the null hypothesis that there was no relation between all the treatment groups and the behaviour breakdown observed. The data have been set out in a 2 by 2 table in Table IV.

TABLE IV

	Run	No Run	
Groups I to IV	20	0	20
Groups V to VIII	0	20	20
	20	20	40

Table IV yields a $\chi^2 = 36{\cdot}1$ with 1 degree of freedom using Yates correction for continuity, a result comfortably beyond the 0·01 level of significance.

Animals in experimental treatments VII and VIII, *i.e.*, drug dosages of 2·5 mg./kg. and 5 mg./kg., were tested for the time of recovery. The criterion of recovery had to be an approximate one. The reason for this was that between 18 and 24 hours rats may make one run, eat ravenously for the permitted 15 seconds, and then relapse, making no further attempts to move. At this hour the effect of auditory stimulation in some cases induces a locomotor response, and not in other cases. To offset this recording difficulty the following criterion of recovery was adopted. Each rat had to make three successive hourly runs without the auditory stimulation. The middle run was then taken as the criterion of recovery (Table V). An examination of the recovery times seems to indicate that it is influenced by the drug concentration used in the treatment. The non-parametric, Mann-Whitney test (Siegel, 1956) can be used to determine the assumption that the treatment of Experimental Group VIII (5 mg./kg.) will have the slower rate of recovery. This test yielded a U = 3. This result can be held to be significant at the 3% level on the one-tailed test (Siegel, 1956). Only latency times are specifically dealt with in this section. Running times are not considered, as they yielded very much the same level of information, without adding fresh substance to the arguments raised in the discussion.

TABLE V

RECOVERY AFTER RESERPINE ADMINISTRATION

Time Hour after Injection	Treatment									
	No. Rats Given 2·5 mg./kg.					No. Rats Given 5 mg./kg.				
	1	2	3	4	5	1	2	3	4	5
18	–	–	–	–	–	–	–	–	–	–
19	–	–	–	–	–	–	–	–	–	–
20	–	–	–	–	–	–	–	–	–	–
21	–	–	–	–	–	–	–	–	–	–
22	–	–	–	–	–	–	–	–	–	–
23	–	–	–	–	–	–	–	–	–	–
24	–	1	–	1	–	–	–	–	–	–
25	1	2	–	2	–	–	1	–	–	–
26	2	3	–	3	1	–	2	–	–	–
27	3	–	–	–	2	1	3	–	–	–
28	–	–	1	–	3	2	–	–	–	–
29	–	–	2	–	–	3	–	–	1	–
30	–	–	3	–	–	–	–	–	2	1
31	–	–	–	–	–	–	–	–	3	2
32	–	–	–	–	–	–	–	1	–	3
33	–	–	–	–	–	–	–	2	–	–
34	–	–	–	–	–	–	–	3	–	–
35	–	–	–	–	–	–	–	–	–	–
36	–	–	–	–	–	–	–	–	–	–

Discussion

From an examination of the results it is clear that there is a substantial delay period before the action of reserpine on behaviour becomes effective. This delay period terminates approximately two hours after intraperitoneal injection. There is very little scatter in these results. The actual time in which the onset of the drug's action occurred, as measured by latency scores, was very rapid, although neurological indications appeared very much earlier. Once the onset has occurred there was no intermittent remission observed during the experimental period. The effect of high levels of white noise was negligible, and perhaps interesting in that it produced no behavioural response.

The behavioural changes produced by reserpine can be safely attributed to the use of this alkaloid. The use of an injection vehicle control has shown that the effect is only apparent in the presence of the reserpine. At the same time the effect cannot be considered to be due either to the injection or to the fluid volume *per se* as shown by the sterile water control group.

There is relatively greater variation in the recovery times than in the onset. Recovery, as was defined here, is operational, namely, the mean hour of three successive responses. It is suggested by the data that recovery is a function of the amount of drug injected.

Of greatest interest are the relatively long-term and drastic behavioural changes which are induced by reserpine. It is becoming reasonably clear that the peculiar effects on the central nervous system associated with reserpine are due to the substance itself. Sheppard, Lucas, and Tsien (1955) injected radioactive reserpine intravenously (400 μg.) into adult male rats. They demonstrated that reserpine

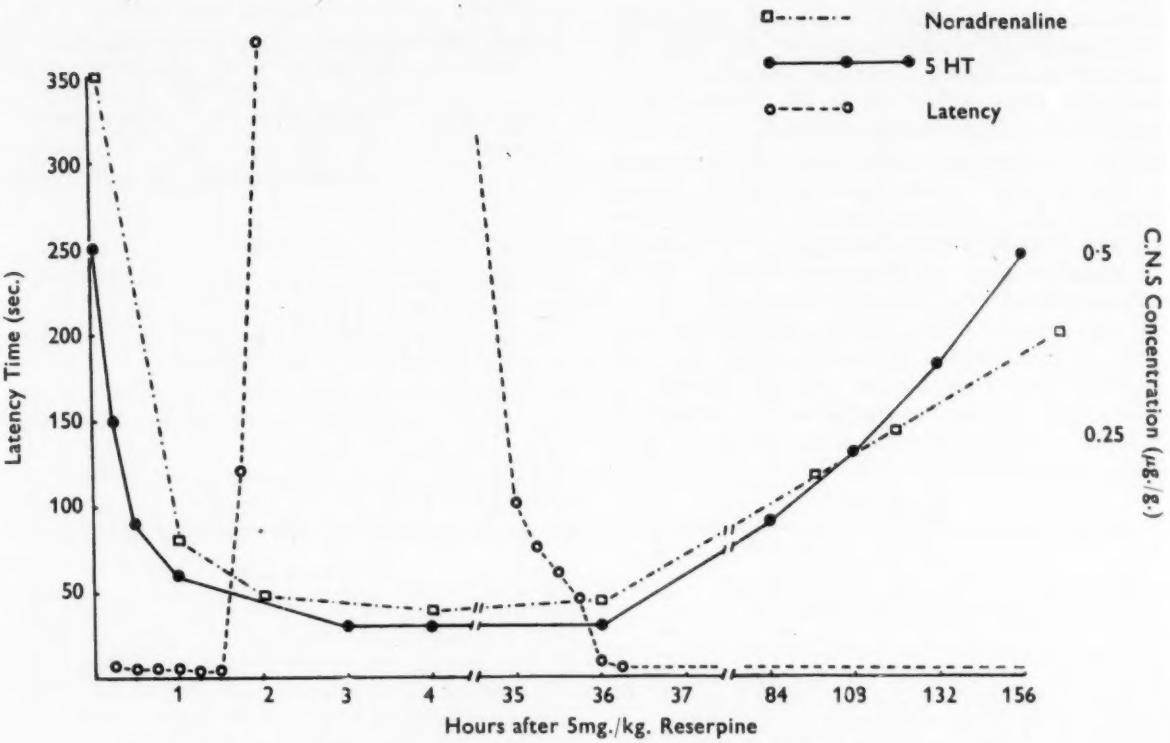

FIG. 3.—Mean latency after 5 mg./kg. reserpine in relation to cerebral 5 HT and noradrenaline.

disappeared extremely rapidly from the blood stream, there being only 0·3% remaining two minutes after injection. There was no cerebral concentration of ^{14}C-labelled reserpine detectable six hours after its administration. However, as has been demonstrated, some central disturbances induced by this drug persist for a remarkably longer period than could be accepted as being due directly to the presence of reserpine. The latency and persistence of the sedative and tranquillizing reaction can most conveniently be examined at the biochemical level.

Some authors have speculated that those observed disturbances that cannot be attributed to reserpine are linked to disturbances in 5 hydroxytryptamine (5 HT) and noradrenaline metabolism. Hess, Shore, and Brodie (1956) have demonstrated that reserpine has a 5 HT-releasing property for rabbit brain tissue. The 5 HT content, which is normally 0·55 μg./g., fell rapidly after intravenous injection of reserpine (5 mg./kg.) so that by 30 minutes the brain 5 HT had declined about 75% and in four hours about 90%. This low level of brain 5 HT persisted for 36 hours and then slowly rose to normal values over seven days.

The 5 HT-releasing property of reserpine is neither tissue nor species specific. Paasonen and Vogt (1956) reported that as little as 0·5 mg./kg. reserpine reduced the level of 5 HT in the dog brain to vanishing amounts. Using human subjects, Haverback, Shore, Tomich, and Brodie (1956) have shown that the successive administration of very small doses of reserpine reduces the capacity of blood platelets to retain 5 HT, indicating that reserpine can act in a cumulative manner. The authors were also able to demonstrate this cumulative effect of small doses of reserpine on rabbit brain tissue. In a human study, Hardisty, Ingram, and Stacey (1956) reported that 1 mg. intramuscular reserpine removed virtually the whole 5 HT in blood platelets, and at the same time impaired the ability of platelets to absorb 5 HT. These findings have been confirmed for the rat by Erspamer (1956), who was one of the original discoverers of 5 HT as a normal body constituent.

Similar findings have been reported on the effects of reserpine on cerebral noradrenaline concentration. Holzbauer and Vogt (1956) found that reserpine (0·4 mg./g.) reduced the noradrenaline concentration of the cat's hypothalamus from its normal 1·4 μg./g. fresh tissue to between 0·2 and 0·6 μg/g. These results have been confirmed by Shore, Olin, and Brodie (1957) in the rabbit.

An attempt can be made to relate these biochemical findings to the behaviour. In Fig. 3 the graph is designed to show the time relationship between the fall in 5 HT and noradrenaline con-

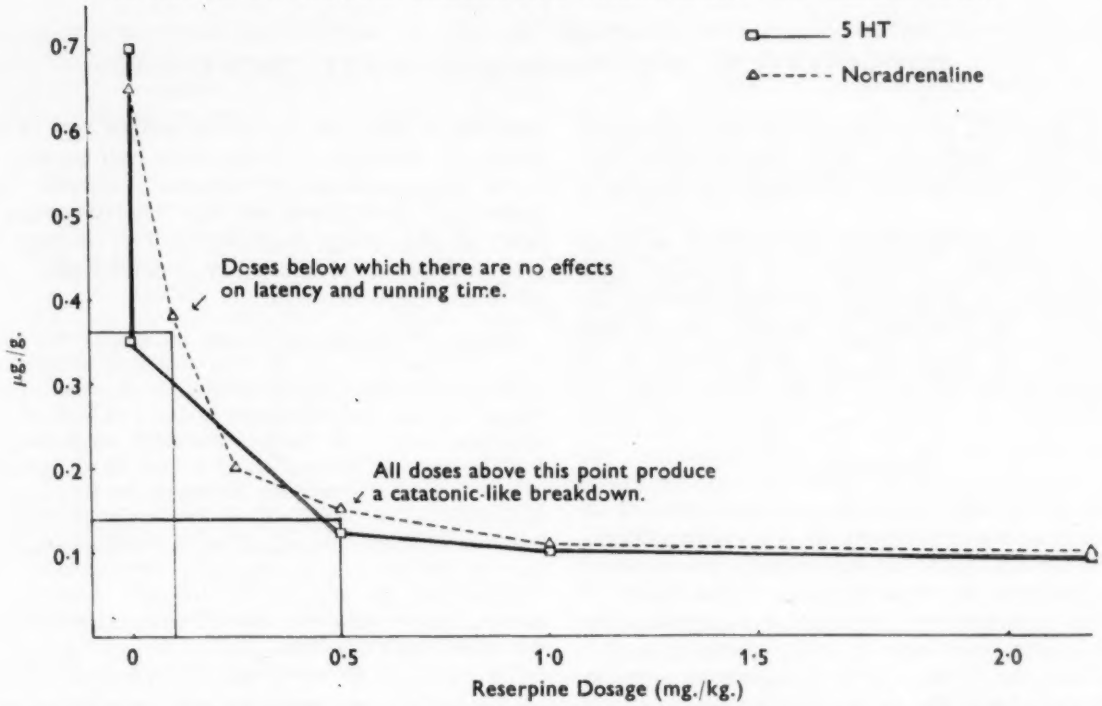

FIG. 4.—Brain concentration of 5 HT and noradrenaline four hours after varying doses of reserpine, and the effect of varying doses of reserpine on behaviour.

centrations and the rates of recovery in conjunction with the latency data reported in this experiment. With the precaution in mind that this approximation involves different species it can be seen that the behavioural effects are roughly correlated to specific changes in the biochemistry of the central nervous system rather than to the specific effect of reserpine. A second interesting correlation can be made between the dosage levels of reserpine found in this experiment to have dramatic consequences on behaviour and the noradrenaline and 5 HT levels in the brain-stem four hours after the administration of equivalent doses (Fig. 4).

One important factor must be considered in evaluating these biochemical effects in relation to behaviour. While in the case of 5 HT there is apparent depletion in cerebral concentrations there is, however, actually an increased turnover rate of the compound as distinct from noradrenaline activity which only shows a depletion. Udenfriend, Weissbach, and Bogdanski (1957) have provided evidence that potentially more 5 HT can be destroyed than can be made in a given time. As 5 HT continues to be formed, though no longer bonded, owing to the reserpine effect, there exists not only a high level of 5 HT activity, but also a very rapid turnover of this substance. These authors have demonstrated with radioactive studies that the half-life of cerebral 5 HT is of the order of one to two hours. Thus, though at any particular moment the 5 HT assay reveals a relatively low cerebral concentration of 5 HT after the administration of reserpine, in point of fact the activity and turnover is increased many times.

From the consideration of the biochemical and behavioural evidence the following at least tentative conclusions can be drawn :—

(1) The behavioural decrements found with reserpine treatment cannot be ascribed to the specific action of this drug *per se*.

(2) The decrements as measured in this experiment are related in time to changes in 5 HT and noradrenaline activity in the central nervous system.

(3) There is some indication that while noradrenaline levels are relatively depleted there is an increased turnover of cerebral 5 HT.

The effects of reserpine on other amines has as yet not been investigated, though it is not unlikely that these would also show some change. The behavioural disturbances induced are associated with a number of marked physiological changes, such as a fall in deep body temperature and an extrapyramidal syndrome and a blockade of the sympathetic system. In Part II these physiological factors will be examined and some attempt will be made to examine these as the possible causal factors underlying the behavioural response of the rat to reserpine.

PART II:
PHYSIOLOGICAL AND PHARMACOLOGICAL MECHANISMS

The mediating physiological and pharmacological mechanisms which may have been causally connected with the behaviour disturbance are the subject of Part II.

Three sets of experiments are reported in which several plausible hypotheses are advanced and investigated. In all cases the rats were tested for the effects of the treatment on latency and running times, as this procedure has been shown to be sensitive to the effects of drugs which affect behaviour.

Experiment I

One of the most striking syndromes induced by reserpine is an overactivity of the extrapyramidal motor system. This is indicated by the presence of a rhythmic alternating tremor in the region of the head and neck with an apparent paralysis of the limbs. This latter state is also associated with a rigidity in the limbs on passive movement. Owing to the disturbance the rat can be placed in catatonic-like postures. Similar accounts have been given of patients overdosed with reserpine (Kinross-Wright, 1955). Such patients have developed a condition simulating paralysis agitans with paralysis of volitional movement. Spontaneous recovery occurred when the drug was withheld from patients. In these circumstances it was thought not unlikely that the total behaviour breakdown found in the experimental situations with the rat may be attributed to a motor paralysis of central origin.

Experimental neurophysiological studies implicate the involvement of subcortical structures in the aetiology of paralysis agitans. Jenkner and Ward (1953) found that high frequency electrical stimulation of any part of the medial reticular formation of the brain-stem in monkeys produced a rhythmically alternating peripheral tremor analogous to paralysis agitans. These experimentally evoked tremors could be reduced or abolished by the administration of anticholinergic drugs, in particular those drugs which are clinically most useful in the symptomatic and palliative treatment of Parkinson's syndrome. These results were confirmed and elaborated by Rinaldi and Himwich (1954). Rinaldi and Himwich (1955) were also able to show that reserpine administration (0·05 mg./kg.) produced an altered E.E.G. and demonstrated that this arose from an activating system which included the reticular formation.

It was supposed largely on empirical grounds that, if remission of symptoms can be produced with atropine in both the clinical condition and in the simulated disorder, a similar effect may be derived in the pharmacologically induced condition. The hypothesis formulated was that the symptomatic relief of the motor condition in the rat may be instrumental in producing a "normalized" behavioural response.

Design.—This experiment took place over five days. One rat from each of the two treatment orders was employed on every experimental day. In the experimental design five rats were randomly assigned to each of two treatment orders. In the first treatment order atropine was administered, followed an hour later by the injection of reserpine. This treatment was succeeded by a control injection of water. In the second treatment order a control injection of water was administered followed an hour later by the injection of reserpine. This treatment was concluded by the injection of atropine. Latency and running time measures were taken quarter-hourly throughout the experiment.

The design can be graphically presented as follows:—

Group	Time in Hours								No. of Animals Treated
	0	1	2	3	4	5	6	7	
A	Atropine			Reserpine			Water		× 5
B	Water			Reserpine			Atropine		× 5

The design serves the twofold purpose of testing whether atropine had a prophylactic and/or therapeutic effect on reserpine-induced locomotor disturbance, and at the same time permits the two treatment orders to be used as mutual controls.

The drug dosages were made up as follows: Reserpine, 5 mg./kg., and atropine sulphate in a distilled water solvent, 120 mg./kg., were made up in 1 ml. volume and injected intraperitoneally. Distilled pyrogen-free water was administered as a control in a volume of 1 ml. The use of 5 mg./kg. reserpine was designed to permit performance comparisons to be made with the data from previous experiments. In particular the catatonic-like behaviour found with the use of this dosage level could be reproduced. The dosage of atropine sulphate was determined on normal scrub rats. These animals were injected with varying doses and tested for any resultant violent motor excitation. It was found that with doses much over 150 mg./kg. some excitation occurred. The actual tolerance level of atropine in the rat is very high, in the region of 500 mg./kg. intraperitoneally (Willberg, 1914).

Results.—The results when considered from both the viewpoint of latency and running time are negligible. All rats, irrespective of the treatment order, succumbed to the effect of reserpine between one and a half and two hours after administration

The mean data are set out in Table VI. The rats remained inactive for up to 36 hours. The effect of the noise generator on three of the rats treated with atropine was to induce an audiogenic seizure.

TABLE VI
MEAN LATENCY AND RUNNING TIME

Hour	Trial No.	A		B	
		Latency	Running Time	Latency	Running Time
—	1	4	2	5	3
—	2	3	3	7	4
1	3	7	2	5	6
—	4	6	4	4	2
—	5	11	4	6	7
—	6	18	9	15	6
2	7	227	78	162	64
—	8	370	—	321	—
		Experiment terminated.			

Group A treatment order (atropine–reserpine–water).
Group B treatment order (water–reserpine–atropine).

Discussion.—The results are clearly against the hypothesis as formulated. It is therefore necessary first to consider the efficacy of the atropine treatment, and secondly the premises on which the hypothesis was founded.

The failure of atropine to alter the effects of reserpine treatment could be considered as being due to the inadequacy of atropine *per se*. Ambache (1955), in his review on the use and limitations of atropine, lists a number of possibilities which could account for specific resistance to atropine, *e.g.*, the presence of the specific enzyme atropinesterase. These, however, are not applicable in this case for a number of reasons; for example, atropine produced a pupil dilatation and appeared to inhibit salivary secretion which was a feature of reserpine medication. The administration of atropine appeared to reduce the incidence of spontaneous hyperkinetic movement, catatonic-like positioning became impossible, and resistance in the limbs was not felt on passive movement. From these factors it can be assumed that atropine had an effect on the organism, but not the specific effect anticipated, namely, a recovery in normal movements. It is therefore highly probable that the premises concerning the effects of reserpine treatment require re-examination.

The basic assumption made in treating paralysis agitans, whether in the case of the clinical entity or experimentally produced lesions, is that damage in the lower diencephalon interrupts the motor fibres into the medial reticular formation. Empirically it is found that the resulting motor disorder can be ameliorated by the administration of atropine or atropine-like agents. Jenkner and Ward (1953) suggested that the deafferented cells in the reticular formation subsequently become hypersensitive to the locally liberated acetylcholine, and further that atropine exerted an anticholinergic effect at this site. These arguments tend to indicate that the motor disorder is related to the predominating effects of the cholinergic neurohumoral mechanism. Reserpine, however, produces no lesions (except perhaps in the biochemical sense) in the basal ganglia, nor is the neurohumoral apparatus necessarily adapted to a higher level of cholinergic activity. However, changes in neurohumoral balance do occur as a consequence of administration of reserpine. These changes are predominantly in the direction of a diminution in the sympathetic or adrenergic neurohumoral activity. A reduction in the adrenergic system produces symptoms which could be described as being parasympathetic-like. With this point in mind it could be considered that the approach employed in this experiment is in the wrong direction, namely the use of an anticholinergic agent should be replaced with the use of an adrenergic-like agent. Some support for this argument will be found in a subsequent experiment reported in this paper.

The hypothesis that the extrapyramidal syndrome observed as a consequence of reserpine administration is related to the cessation of locomotor behaviour is not justified by the findings in this experiment. Atropine was found to alleviate the hyperkinesis, but did not restore the rat to a " normal " level of behaviour. It was also considered probable that a different direction would have to be taken to locate the neurohumoral factors which could be causal to the reserpine-induced behaviour disturbance.

Experiment II

An alternative mechanism proposed was one arising out of profound changes in thermoregulatory control. Invariably, reserpine depresses the body temperature, the effect being central in origin. There is considerable evidence in the general literature (Burton and Edholm, 1955) which confirms common experience that only a moderate change in deep body temperature (as in fever) results in profound confusion in mental processes. A hypothesis was set up in the following terms. Reserpine induces a severe change in body temperature while simultaneously affecting behaviour. The restitution of the deep body temperature to normal levels may indicate any causal relationship which may exist between temperature regulation and the behaviour observed. In the event that any causal relationship can be found, it may be possible to investigate whether this results from a mal-functioning in some

higher nervous process, or constitutes a motivational failure.

There are two ways in which this problem can be examined. In both methods the essential technique is to reverse the thermal gradient in a manner such that the animal's deep body temperature returns to normal. First, it is possible to reverse the external thermal gradient, whereby the rat gains heat, and secondly, one can alter the thermoregulative mechanism whereby the rat generates more heat.

In order to investigate this problem the first experiment comprised an attempt to alter the external thermal gradient. The requirements are basically simple, but were difficult to make effective. Five rats were treated with 5 mg./kg. reserpine. By six hours, the deep body temperature had fallen by 2 to 3° C. These animals were placed in the latency box of the apparatus, under conditions and training procedures that were identical with those used hitherto. The back of each experimental animal was approximately 2 in. from a continuously radiating heat source. The laboratory was thermostatically regulated, the room temperature being set at 20° C. ± 3° C. Level with the rat's back, an ambient thermometer was placed in such a manner that the distance of the heat source could be varied to give a constant temperature of 60° C. It was found that a distance of 6·5 cm. between the heat source and the rat gave a steady environmental temperature of 60° C., within 7 minutes 45 seconds. This gave a positive heat gradient from 60° C. on the fur to a deep body temperature of approximately 35·4° C. It was found in practice that within 15 minutes the deep body temperature rose to 37·5 and 38·5° C. Rats were continuously observed from 30 to 45 minutes with a raised deep body temperature. The observations made with this technique gave a clear but only descriptive picture. No behavioural changes occurred which could be associated with thermoregulatory failure as such. It was found that animals made no attempt to initiate locomotor behaviour, demonstrated no interest in food, and were still catatonic-like when handled.

There were, however, very many objections to this crude procedure. Rats with hypothermia are more likely to remain within the immediate vicinity of the heat source rather than move along the runway, even if the length of the runway has the same positive thermal gradient. This observation confirms the results found by Schwartzbaum (1955) that rats treated with reserpine showed marked thermal preferences, in that they remained in the vicinity of a given heat source. It was consequently thought desirable to attempt an alternate means of readjusting the deep body temperature by artificially raising it internally.

There are a number of clinical disorders in which curative fever treatment is employed, *e.g.*, neurosyphylis. For this malarial treatment has been conventional. In recent years it has been found advantageous to use specific pyrogenic agents. The agent used in this experiment was "pyrifer", an albuminous substance obtained from *Bact. coli.*, a non-pathogenic race of microbes. A number of preliminary trials were attempted on scrub rats in order to determine the number of units (each unit = 1,000,000 germs per ml.) required to raise the reserpine-depressed temperature to a "normal level", *i.e.*, 37·5° C. The observation made with a population of normal but identical strain showed that the mean rectal temperature was 37·5° C. with a variation ± 3° C. This substantially agrees with the observations made by Pembrey (1895) on albino rats. It was found in practice that 1,000 units injected intravenously three hours after reserpine raised the temperature to "normal levels". It was considered desirable to compare the deep body temperatures of one group of rats, while simultaneously testing the behaviour on a litter mate group.

Design.—Five male litters were obtained from the same source as in all previous experiments. Each group comprised four rats; litters were divided randomly but evenly into four populations and assigned orders. Group A was composed of animals which were treated with 5 mg./kg. reserpine. After three hours, 1,000 units of pyrogenic agent were given intravenously. Rectal temperatures were recorded every hour for eight hours on the first day. On the second day temperatures were recorded every three hours. Group B was composed of animals which were treated with 5 mg./kg. reserpine. After three hours an equivalent volume of pyrogen-free distilled water was injected intravenously. Observations were made as in the case of Group A. Group C animals were treated with 5 mg./kg. reserpine, and after three hours all animals received 1,000 units of the pyrogenic agent. Observations on latency and running times were made every half hour for eight hours. Group D animals were treated with 5 mg./kg. reserpine. After three hours all rats received 2 ml. pyrogen-free water intravenously. Observations were made as in Group C above. The animals in Groups C and D were trained and treated in the fashion reported in all previous experiments. The environmental temperature throughout the experiment was 20° ± 3° C. for all groups.

Results.—The effect of the treatment as outlined in groups A and B may be found in Table VII and groups C and D in Table VIII.

It will be readily seen that no difference exists worthy of note between the onset rate in the reserpine behaviour decrement of either group C or D. Moreover, there was no change in the total cessation

TABLE VII

MEAN RECTAL TEMPERATURE IN TWO GROUPS EACH OF FIVE RATS

Hour	Treatment	A	B
	Pre-reserpine temperature	37·3	37·5
1	Reserpine temperature	36·1	36·6
2		36·5	36·7
3		36·9	36·3
4	Intravenous pyrogen	37·4	36·6
5		37·3	36·5
6		37·3	36·3
7		36·6	35·8
8		35·8	35·9

Group A (reserpine, 5 mg./kg. and 1,000 units pyrogenic agent).
Group B (reserpine, 5 mg/kg. and 2 ml. pyrogen-free water).

TABLE VIII

MEAN LATENCY AND RUNNING TIMES IN TWO GROUPS EACH OF FIVE RATS

Trial No. Half-hour Spaced after Injection	C		D	
	Latency	Running Time	Latency	Running Time
1	9	3	7	2
2	5	2	6	4
3	18	5	8	11
4	274	—	290	—
	Total cessation of all responses			

Group C (reserpine, 5 mg./kg. and 1,000 units pyrogenic agent).
Group D (reserpine, 5 mg./kg. and 2 ml. pyrogen-free water).

of locomotor activity after two hours, *i.e.*, trial no. 4. At no time during the subsequent trials spaced every half hour did the rats respond to the experimental requirement.

It will be noticed that the effect of 1,000 units of pyrogen was instrumental in raising the mean rectal temperatures 1·5 to 2° C. in one hour or less. This quasi-normal level of heat generation was maintained for two hours, after which the temperatures fell back to the previous low reserpine level. This effect may be seen in graph form (Fig. 5).

Discussion.—It is reasonably clear that the experiment yielded no results which indicate a necessary connexion between deep body temperatures and the behaviour examined. The prevailing deep body temperature may indeed be relevant to any behavioural investigation, but in the particular case of reserpine the lowered body temperature is probably not the determining factor. These observations are in marked contrast to those made by Lessin and Parkes (1957). These authors concluded in an experiment conducted with reserpine on mice that reduced locomotor activity and sedation is

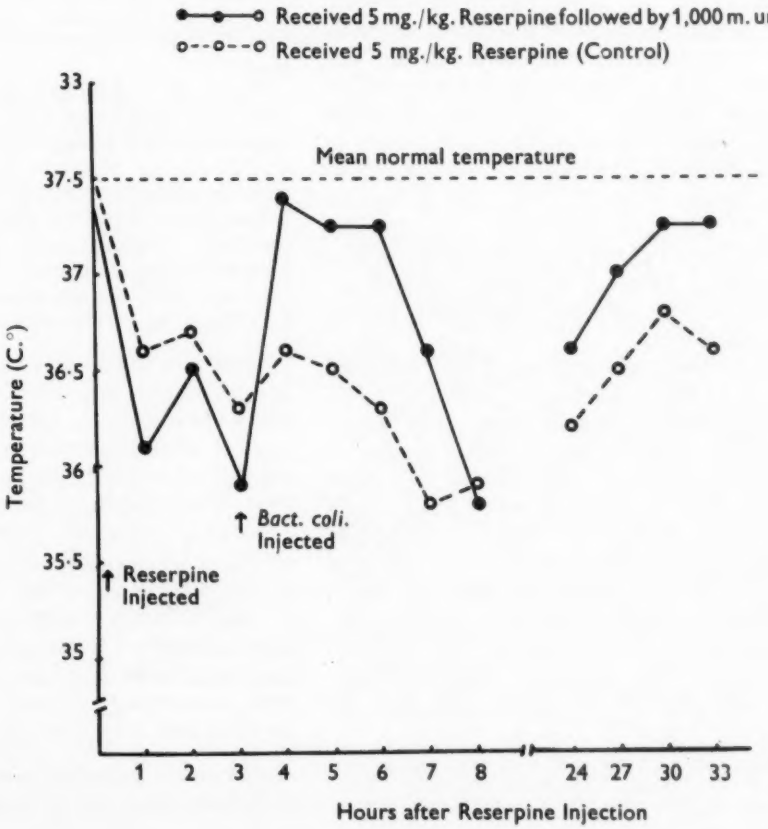

FIG. 5.—Rat rectal temperature (mean of five rats/group).

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proportional to the degree of hypothermia. By raising the ambient temperature they found that reserpine was no longer hypothermic or sedative. However, these authors were testing the effects of reserpine on prolonged pentobarbitone hypnosis which entails the problem of drug interaction.

It is obvious that the techniques employed to test this hypothesis were inefficient. However, through these experiments and many pilot attempts no evidence could be produced which warranted taking this problem any further.

Experiment III

The third alternative mechanism proposed arose out of considerations involving the general pharmacological properties of reserpine. The general conclusions derived from these studies tended to indicate that reserpine induced a shift in the normal balance between the cholinergic and the adrenergic neurohumoral systems (Bein, 1956). In particular it was suggested at the time that reserpine inhibits the sympathetic outflow and has no particular stimulating property for the parasympathetic hypothalamic centre. The result of reducing sympathetic activity is an increase in parasympathetic tone. It is possible to consider that by offsetting the reduced activity of the adrenergic neurohumoral mechanism, as for example with a sympathomimetic agent, that a balanced neurohumoral picture will result. Under these circumstances the behavioural components of reserpine administration could be expected to show a remission for the duration of the action of the sympathomimetic drug. A secondary consideration for which some material may be obtained from such an experiment concerns the problem of isolating out the plausible neurohumoral factors involved. There is as yet no reliable information as to the chemical mediators in the central nervous system.

A suitable sympathomimetic agent was obtained from CIBA.* Methyl phenidate (" ritalin ") was prepared as a synthetic analeptic drug. The stimulating properties of the central nervous system of this phenidate compound are similar in many respects to that of benzedrine and caffeine with several important differences. Methyl phenidate produces almost no peripheral sympathomimetic effects, *e.g.*, there is no significant effect on blood pressure, respiration, and heart rate. Further, this drug produces none of the euphoric effects found with benzedrine or the circulatory reactions associated with caffeine. It was considered that the suitability of methyl phenidate as a reserpine antagonist could rest principally with the drug's specific central sympathomimetic effect.

The hypothesis was considered in the following terms. Reserpine shifts the neurohumoral balance toward an adrenergic deficit, at the same time inducing a marked behaviour change. The administration of a suitable sympathomimetic agent could redress this balance and restore the animal's capacity to respond to the experimental requirements.

Design.—The subjects of this experiment were 10 male rats. One control and one experimental group were employed. One animal from each group was taken for each of five replications. Rats were randomly assigned to two treatment groups in equal numbers, there being five rats per treatment. All rats were given 5 mg./kg. reserpine intraperitoneally, and observed for latency and running times every 15 minutes for six hours. In the experimental group a further injection of 10 mg./kg. methyl phenidate intraperitoneally was given at the beginning of the seventh hour from the start of the experiment. Latency and running time were recorded every five minutes for one hour. The control treatment group received 1 ml. of saline intraperitoneally at the beginning of the seventh hour from the start of the experiment. Latency and running times were observed for one hour at five-minute intervals. From the eighth hour after the experiment rats were tested every 15 minutes until 12 hours had elapsed from the start of the experiment.

The standard dose of 5 mg./kg. of reserpine was used. The administration of 10 mg./kg. methyl phenidate was determined by a series of preliminary trials in which it was found that doses of the order of 12 mg./kg. and above produced some symptoms of locomotor excitation. Doses below 10 mg./kg. were found to affect reserpine pre-treated rats in a manner too ambiguous to evaluate with the testing procedure used. The dosage employed was only 10% of the dosage level required for an L.D. 50 mg./kg. for the equivalent route of administration.

Results.—The results may be found in Table IX. It is apparent that the effects of methyl phenidate administration are distinctly different from the control saline-injected group. No alteration in the state of reserpine-treated animals was found at any time after administration of saline. The effect of methyl phenidate is extraordinarily rapid, having an onset of between two and three minutes. The duration of the drug's effect is approximately 15 to 20 minutes after which the effects of the administration of reserpine slowly reappear. The data have been graphed (Fig. 6). Running times were immediately affected; rats were able to move on their first trial after methyl phenidate.

Discussion.—Methyl phenidate appears to have a high specificity for the cerebral environment. The

*Ritalin was kindly supplied by Dr. K. Pittman, CIBA Laboratories, Horsham, Sussex. The " ritalin " crystals are soluble in a saline vehicle.

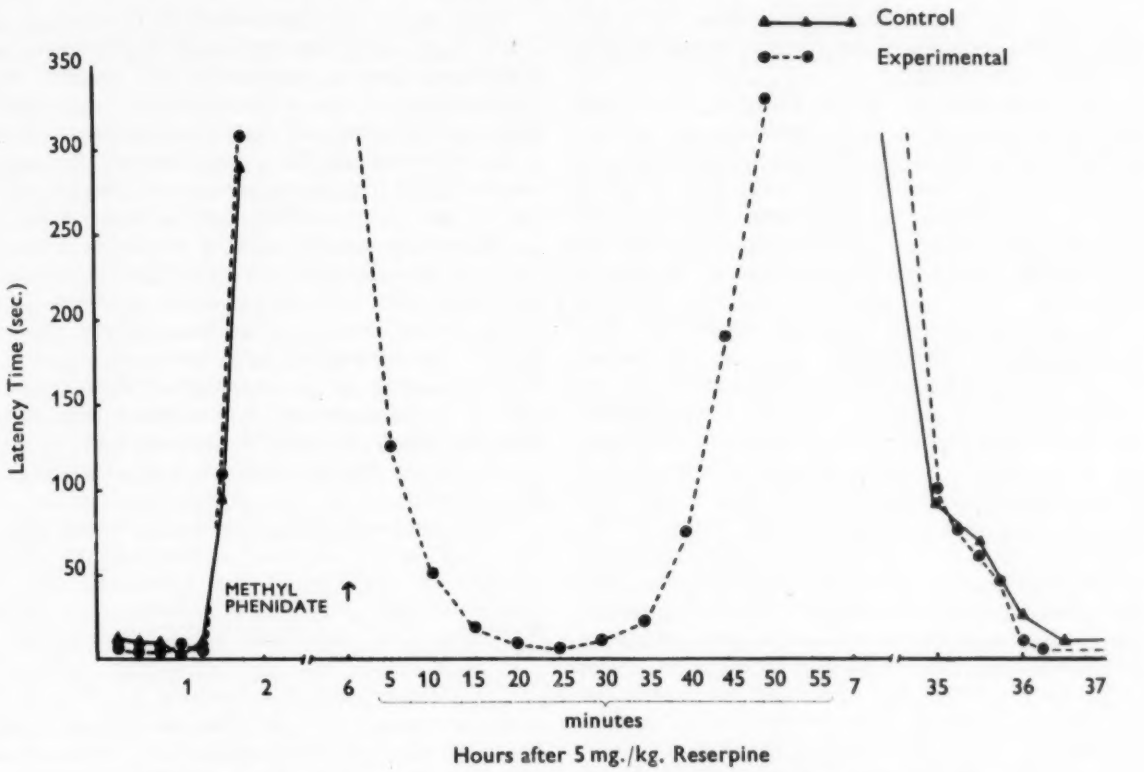

FIG. 6.—The mean latency of the effect of 10 mg./kg. methyl phenidate six hours after 5 mg./kg. reserpine.

TABLE IX

MEAN LATENCY AND RUNNING TIME

Hour	Trial No.	A		B	
		Latency	Running Time	Latency	Running Time
1	1	8	4	6	3
	2	5	5	5	2
	3	5	3	4	4
	4	4	3	5	2
2	5	7	4	6	3
	6	6	2	5	2
	7	93	47	118	63
	8	294	—	311	—
		Total cessation of all running behaviour		Total cessation of all running behaviour	
7	1	—	—	123	12
	2	—	—	56	17
	3	—	—	21	13
	4	—	—	12	4
	5	—	—	5	7
	6	—	—	11	3
	7	—	—	24	2
	8	—	—	77	8
	9	—	—	180	31
	10	—	—	340	—
	11	—	—	Total cessation of running behaviour	

Group A control treatment order (reserpine–saline).
Group B experimental treatment order (reserpine–methyl phenidate).

rapidity with which methyl phenidate affects the organism is indicated by the speed (one to two minutes) in which the reserpine-induced ptosis and pupil constriction is replaced by a mild mydriasis with the eyelids open. This shift could be taken as indicative of a change in the neurohumoral balance. The reserpine-induced ptosis started to reappear 15 to 20 minutes after the initial medication with methyl phenidate, and heralded a return to the reserpine behaviour syndrome which did not have its full impact until some 30 to 45 minutes had elapsed. Methyl phenidate has this antagonistic effect irrespective of the time during the reserpine-induced catatonic-like behaviour state it is administered. The drug does not appear to shorten the total length of the reserpine effect.

A difficult problem is to decide whether the reserpine-induced disturbances are exclusively in one neurohumoral direction, namely a depression of the adrenergic system. A number of autonomic indicators show that there is a likelihood that the cholinergic system is simultaneously stimulated. Contemporary experimental evidence is far from being dogmatic about the nature or even the degree of the shift in neurohumoral balance. Recent hypothalamic stimulation experiments on unanaesthetized cats have demonstrated that reserpine appears to affect this area in two ways. It depressed the sympathetic centres in the diencephalon, and

facilitated the parasympathetic centres as determined by the evoked blood pressure (Anand, Dua, and Malhotra, 1957).

Two issues arise out of the foregoing discussion, and these must be at least speculatively treated. These issues embrace first, the role 5-hydroxytryptamine (5 HT) and noradrenaline may play in determining the central neurohumoral balance, and secondly, the influence any ensuing neurohumoral disturbance could be considered to have on behaviour.

In any appraisal of reserpine effects the first consideration to be stated is that the disturbance in neurohumoral balance induced by the drug is not occasioned by its presence as such. It has already been accounted that reserpine is rapidly metabolized out of the system, leaving behind an altered state in a number of cerebral amines (Glow, 1957). The evidence available at the moment leads to the assumption that 5 HT and noradrenaline levels are drastically altered by the administration of reserpine. The question arises as to what role these humoral agents normally play in the brain, particularly as at this moment there is no reliable evidence which would lend to the acceptance of any particular neurohumoral system in the central nervous system. For example, it is not established that acetylcholine, the peripheral neurohumoral transmitter, operates in the same fashion in the central nervous system.

A number of neurohumoral-like activities have been attributed to 5 HT via the release and increased turnover of the substance by reserpine or the administration of the precursor 5 hydroxytryptophan. Some of these effects are a type of sedation, decrease in depth and rate of respiration, reduction in arterial blood pressure, slowing of the heat and a fall in deep body temperature, etc.

From the above effects it could be inferred that 5 HT is normally involved in the regulation of the subcortical centres responsible for alerting, temperature regulation, blood pressure, and similar autonomic functions of the parasympathetic system.

The question may be asked, What is the nature of this 5 HT regulatory function ? Welsh (1957) has to some extent demonstrated that 5 HT or a compound remarkably similar to it has a neurohumoral transmitter role in invertebrates, though a similar function of 5 HT has as yet not been clearly recognized in the central nervous system of vertebrates. Several authors have, however, argued that in the absence of any established alternative the role of a neurohumoral transmitter in the central parasympathetic division of the autonomic nervous system could be assigned to 5 HT (Brodie and Shore, 1957).

The suggestion has also been made that noradrenaline could be the chemical mediator in the central sympathetic division of the autonomic nervous system. In view of the lack of any contrary evidence this could be a reasonable working assumption.

If these views are consistent and reasonable reserpine can be considered to have an effect on the chemical mediators of both the central representations of the parasympathetic and sympathetic systems. In view of this possibility it is not unreasonable to entertain the proposition that the results of treatment with reserpine can leave a profound residual effect on the balance and tone of the autonomic nervous system, the effect being that of depletion of the sympathetic transmitter substance and an augmentation of the parasympathetic transmitter. This imbalance can be compensated for by the administration of a suitable central sympathomimetic agent, methyl phenidate.

PART III:
EFFECTS OF d-LYSERGIC ACID DIETHYLAMIDE AFTER PREMEDICATION WITH RESERPINE

The data concerning the concentrations of the cerebral amines set out in Part II are of particular interest because it is possible to investigate systematically the hypothesis which has linked the action of the hallucinogen lysergic acid diethylamide (LSD-25) with the presence of endogenous cerebral 5 HT.

Repeatedly attention has been drawn to the existence of a strong antagonism between LSD-25 and 5 HT on peripheral excised tissues, such as rat uterus (Woolley and Shaw, 1954). These authors proposed that the peculiar psychological properties of LSD-25 may well arise from a similar antagonism in the central nervous system. A simple experiment to test this hypothesis, by administering exogenous 5 HT, cannot be undertaken as the substance is blocked from the cerebral environment by the selective permeability of the blood-brain barrier. Consequently it has been necessary to consider methods whereby variations in cerebral 5 HT activity could be brought about.

Experiment

In view of the fact that reserpine destroys the 5 HT bonding capacity of cerebral tissues, inducing thereby an alteration in the level of the activity of the substance (Brodie, Pletscher, and Shore, 1956; Udenfriend, Weissbach, and Bogdanski, 1957), it is possible to investigate the effects of LSD-25 during the seven-day recovery period. Under these conditions it should be possible systematically to vary cerebral 5 HT, and test the animal for any differential behavioural reactivity to LSD-25. Clearly the hypothesis generated under these circumstances predicts that the behavioural decrements induced by LSD-25 in the rat will be greater at a time when the least reformation of 5 HT bonding sites has occurred, that is when 5 HT activity is greatest. For this purpose response latencies and locomotor times have been used as behavioural indices using a straight runway technique developed by the author (Glow, 1957).

Design.—This experiment took place over a period of six weeks. As the same population of rats was employed three times, in order to ensure complete recovery between experimental phases, two weeks' recovery was permitted.

All rats received 5 mg./kg. of reserpine administered intraperitoneally. The rats were permitted to " recover " for a given period of time and tested on the apparatus. The experimental animals were divided into two treatment groups. One group received 62·5 μg./kg.; the other group received 250 μg./kg. LSD-25. The control group received an equal volume of distilled water. A control group was subsequently run to demonstrate the effect of LSD-25 treatment omitting the premedication with reserpine. At the conclusion of one experimental phase the rats were permitted to rest from any further drug treatment for two weeks, whereupon the entire population was re-randomized for the next phase.

The phases of the experiment consisted of a given constant time from when the effect of reserpine was no longer apparent, and these were calculated from the times of injection.

Phase 1 was 48 hours after reserpine administration
" 2 " 72 " " " "
" 3 " 96 " " " "

The reserpine pre-treatments were constant in all phases, but the post-recovery period varied progressively by 24 hours over the three phases of the experiment. No consideration was paid to litter mate controls, as it was considered more important to ensure complete randomization over the three phases. This was necessitated by the loss of two animals during the training. The design has been set out in Table X.

During each experimental phase the following procedure was adopted. All animals were run three times without the LSD-25 treatment in order to ensure that the effect of the reserpine pre-treatment was no longer apparent in the latency or running times. The mean of these runs was calculated and regarded as the " normal " performance level of the rat. After treatment had been instigated, *i.e.*, when a given dosage of LSD-25 had been administered, samples of the animals' latency and running times were taken.

TABLE X

EXPERIMENTAL DESIGN SHOWING TREATMENT AND PHASES AFTER TREATMENT WITH 5 mg./kg. RESERPINE

	Treatment		
	1 Control (Water)	2 62·5 μg./kg. LSD-25	3 250 μg./kg. LSD-25
No. of rats in Phase 1 .. (48 hours)	5	5	5
	Re-randomized—two weeks rested (maintained on running schedules)		
No. of rats in Phase 2 .. (72 hours)	5	5	5
	Re-randomized—two weeks rested (maintained on running schedules)		
No. of rats in Phase 3 .. (96 hours)	5	5	5

The drug dosages for both reserpine and LSD-25 were calculated on the basis of the findings made with these drugs in earlier experiments. The use of 5 mg./kg. of reserpine, although a severe dose, was found useful, as in the previous study it was found that all rats recovered within 36 hours. The two LSD-25 treatments represented the lowest and a middle range dose employed in the experiments reported previously (Glow, 1957). The characteristic latency and running times under these dosages were known, and were consequently suitable for comparison.

A noise generator was used under the same conditions as those of previous experiments. Rats were permitted up to five minutes' latency, and then received the stimulus for a further period of two minutes, and if after that time no response was made the trial was terminated. At least 10 observations were made with each subject, though those who had not recovered by the tenth trial were taken on until they had done so. Control runs were only made for seven successive trials. This is in conformity with the number of observations made in the experiments with LSD-25 made by the author and already referred to.

The subjects of this experiment were from a population of 20 rats obtained at weaning from the same source as the group used in the previous experiments. The training apparatus and handling procedures employed were identical with those previously described (Glow, 1957).

Results.—The results are expressed in terms of latency and running times.

Latency.—In Table XI may be found the mean latency times of five rats in each phase of the experiment. This table only records the first seven sample times. From an inspection of the data it is clear that if any important trend is to be found, it is along the phase continuum rather than on the treatment continuum. The severity of the LSD-25 disturbance, irrespective of the amount of the drug

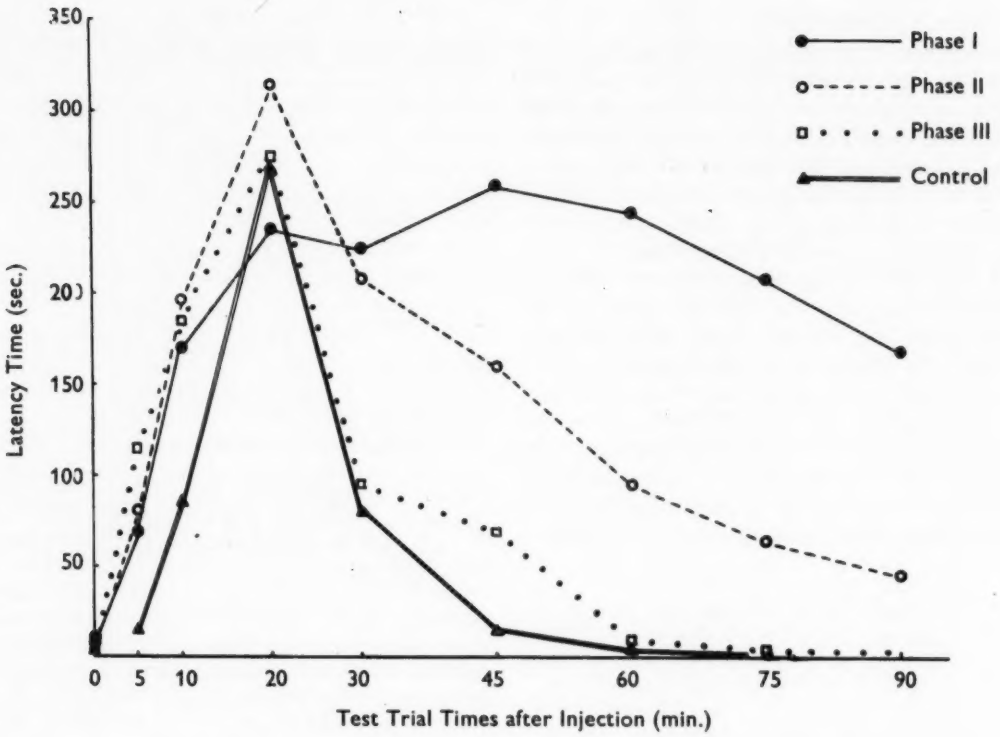

FIG. 7.—Mean latency times for treatment with 62·5 μg./kg. LSD-25 after reserpine.

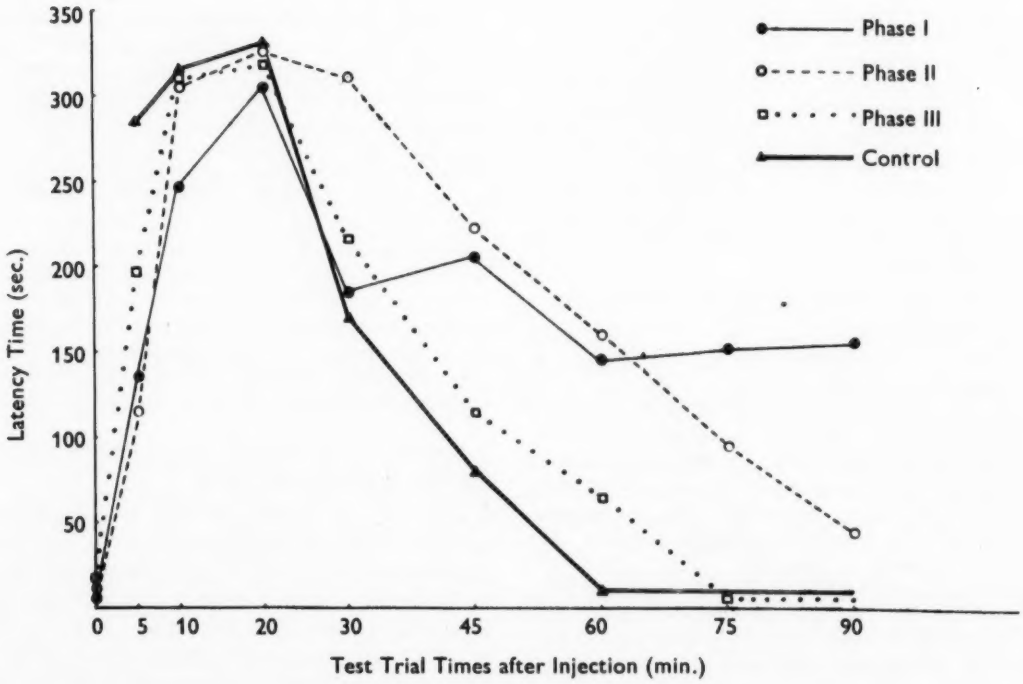

FIG. 8.—Mean latency times for treatment with 250 μg./kg. LSD-55 after reserpine.

TABLE XI

MEAN LATENCY TIMES IN SECONDS OF FIVE LSD-25 TREATED RATS AFTER PRE-TREATMENT WITH RESERPINE

Phase	Test Trial Number	Control Water	Treatment	
			62·5 μg./kg. LSD-25	250 μg./kg. LSD-25
1	1	18	67	134
	2	14	196	244
	3	12	235	304
	4	8	224	185
	5	8	258	206
	6	9	246	148
	7	7	208	153
2	1	6	78	113
	2	7	197	306
	3	5	314	326
	4	5	208	312
	5	4	157	244
	6	5	94	161
	7	4	64	95
3	1	4	115	197
	2	7	176	304
	3	5	274	317
	4	5	94	214
	5	6	69	114
	6	7	9	63
	7	4	4	6

All values taken to the nearest whole number.

administered, decreased with the time permitted to elapse between the pre-treatment with reserpine and the experiment *per se*. An examination of the graph in Fig. 7 (latency curves derived from treatment with 62·5 μg./kg. LSD-25) and Fig. 8 (latency curves derived from treatment with 250 μg./kg. LSD-25) clearly indicates that 48 hours after reserpine pre-treatment the severity persists with only a minor shift towards the value of the control curves. At the same time a comparison may be made with the curves derived from the same dosage level of LSD-25 without any pre-treatment. In the second phase of the experiment, namely 72 hours after reserpine pre-treatment, it is possible to detect a definite trend toward recovery by the sixth or seventh trial, that is, between one and one and a half hours after the start of the LSD-25 treatment. However, it will be noticed that the intensity of the effect induced is still significantly higher than that shown in the control curve obtained from animals which had had no pre-treatment. In the third phase, that is 96 hours after reserpine pre-treatment, the curves have almost the same characteristics as those found in the control curve. The rats clearly exhibit a tendency to recover early, that is between 20 and 30 minutes after treatments had started, and continued steadily to come to normal values. There is little doubt that the intensity and duration of the disturbances produced varies according to the length of the interval permitted to elapse between reserpine administration and LSD-25. There is, however, considerable doubt whether the treatment variable shows an ordered trend. It is noticeable in phase 1

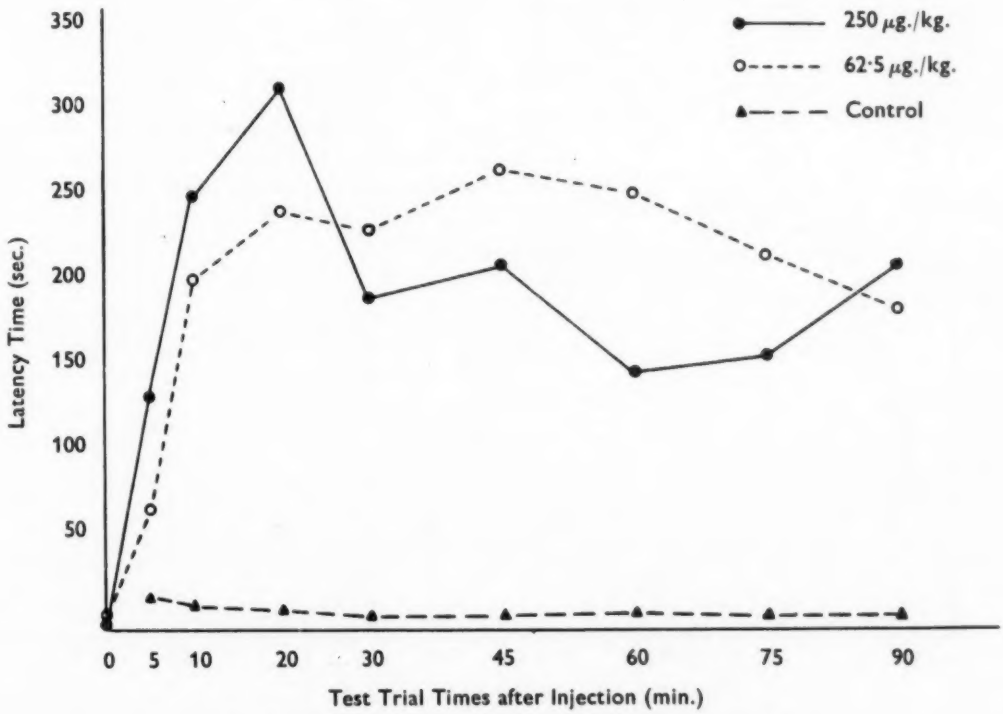

FIG. 9.—Mean latency times during phase I (reserpine pre-treatment).

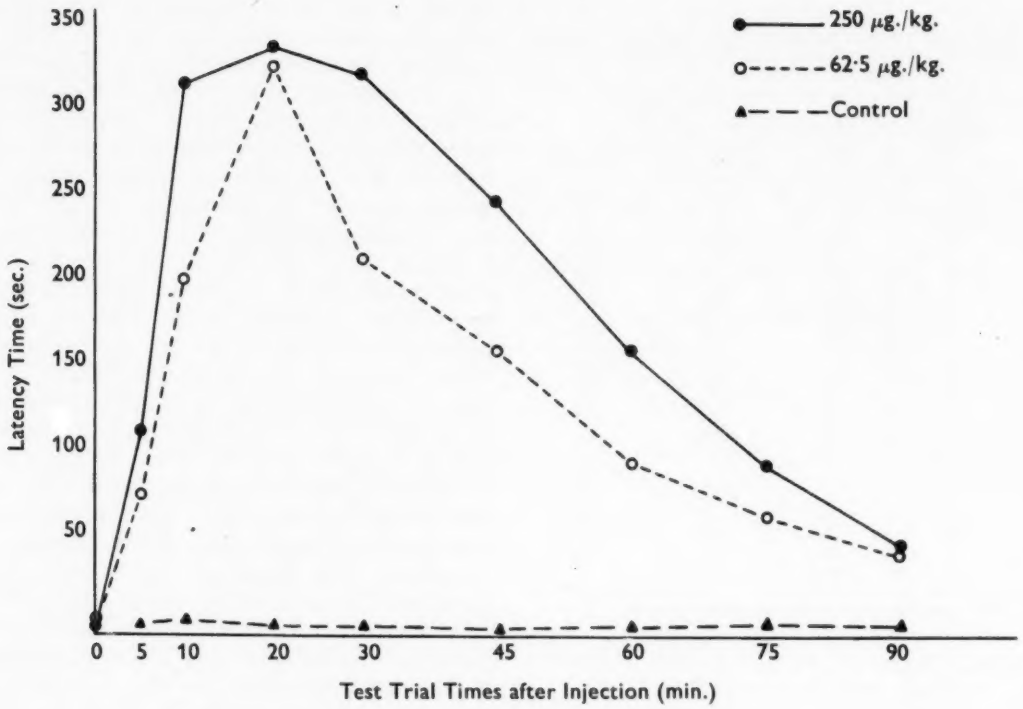

FIG. 10.—Mean latency times during phase II (reserpine pre-treatment).

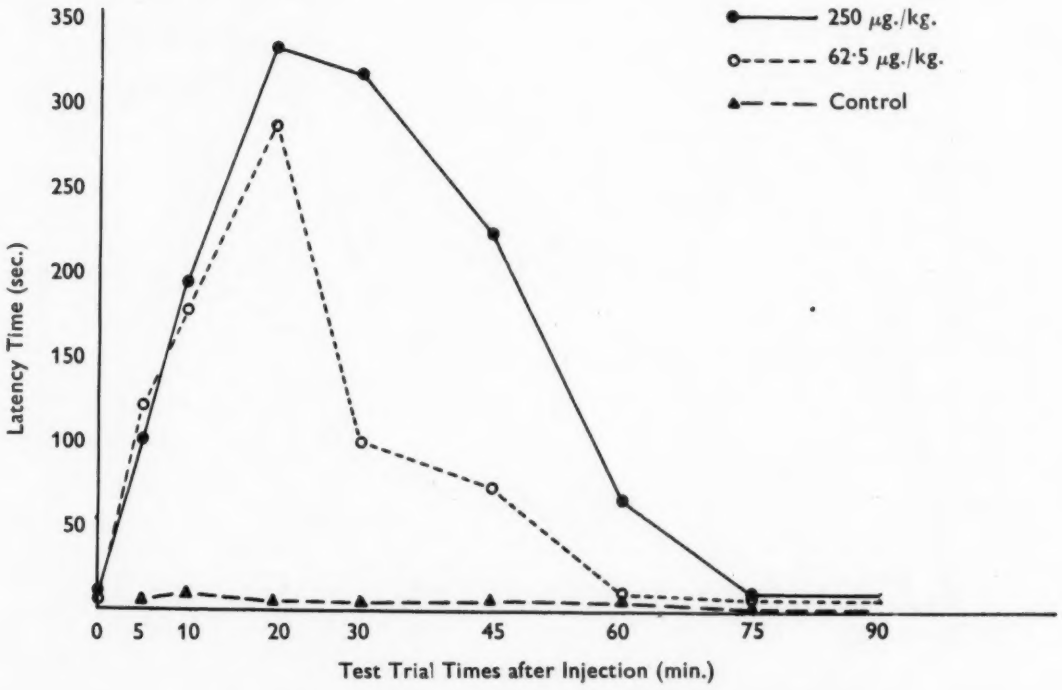

FIG. 11.—Mean latency times during phase III (reserpine pre-treatment)

of the experiment that rats treated with 62·5 μg./kg. LSD-25 showed a disproportionate severity in the behaviour disturbance to those animals treated with four times that dosage, namely, 250 μg./kg. This is clearly demonstrated when the two treatments are plotted for the same phase (Fig. 9). This curious trend does not persist in either phase 2 or phase 3. In these phases the disturbance of the curves plotted is in the expected direction, namely the higher the dose the more intense the disturbance (Figs. 10 and 11).

Another aspect from which the data can be examined is the recovery times from both the treatment and the phase variables. In Table XII may be found the trial number at which experimental animals had recovered. For this purpose the following criterion was employed. When latency times after the LSD-25 disturbance reached nine seconds or less the animal was held to have recovered. The number of that trial was held to be the time taken for the animal to recover from the injection. A comparison and test of significance may be made between the groups to determine whether the various treatments and/or phases significantly affected recovery. The date in Table XII may be a two-way analysis of variance procedure. The specific hypothesis tested was whether recovery from LSD disturbance is a function of the interval between reserpine pre-treatment and LSD-25 administration. The analysis of variance is set out in Table XIII.

It is apparent from the trend found when examining the data for intensity that it holds good when the data are examined from the point of view of recovery, *i.e.*, along the time dimension. The disturbances persist for considerably longer the closer the interval between reserpine pre-treatment and LSD-25 administration. A similar trend is by no means clear when examining the data along the treatment dimension itself. However, the inclusion of the data from the control group in the analysis of variance produces a significant F ratio. This probably is due to the fact that the control lacks variability.

TABLE XII

THE TRIAL AT WHICH RECOVERY OCCURRED AFTER LSD-25 TREATMENT IN RATS PRE-TREATED WITH RESERPINE

Treatment	Subjects	Phase		
		1 (48 hours)	2 (72 hours)	3 (96 hours)
62·5 μg./kg.	1	16	7	4
	2	21	10	4
	3	8	6	5
	4	20	10	4
	5	7	10	7
250 μg./kg.	1	11	8	6
	2	14	10	4
	3	15	11	5
	4	11	13	7
	5	7	10	6
Control	1	4	0	0
	2	2	0	0
	3	6	0	0
	4	3	0	0
	5	0	0	0

TABLE XIII

ANALYSIS OF VARIANCE

Source	Sum of Squares	d.f.	Variance Estimate
Time	678	2	339
Treatment ..	289	2	145
Interaction ..	73	4	18·5
Residual ..	273	36	7·6
	1,313	44	—

F ratio for time = 44 (significant 1%).
F ratio for treatment = 19 (significant 1%).

Running Times.—A brief examination of the running times data can be made from an examination of Table XIV. In the table are the mean running times of five rats in each treatment and phase of the experiment. The table only records the first seven sample times. From the data it can be seen that locomotor times are readily affected by the various phases. This was particularly true in the case of treatment with 62·5 μg./kg. LSD-25 where the separation from the remainder of the scores is greatest. The data have been plotted showing the effect of the treatment on the three phases of the experiment (Figs. 12 and 13). On each graph has been superimposed a curve derived from the same dosage of LSD-25 without reserpine pre-treatment. The overall trend characteristic between treatment level is that with a higher dosage running times are lower, which is indicative of the faster speed with which

TABLE XIV

MEAN RUNNING TIMES IN SECONDS OF FIVE LSD-25-TREATED RATS AFTER PRE-TREATMENT WITH RESERPINE

Phase	Test Trial No.	Treatment		
		Control	62·5 μg./kg.	250 μg./kg.
1	1	12	7	33
	2	5	46	20
	3	4	41	7
	4	3	35	19
	5	5	26	19
	6	4	22	12
	7	3	21	13
2	1	4	12	16
	2	3	13	12
	3	3	17	11
	4	3	20	8
	5	2	22	15
	6	3	16	16
	7	3	11	15
3	1	3	19	22
	2	4	17	24
	3	4	17	11
	4	5	18	8
	5	3	4	8
	6	4	4	7
	7	3	3	6

All values taken to the nearest whole number.

the 250 μg./kg. rats traversed the runway. This trend holds true irrespective of the phase of the experiment. A reasonable sample could be taken at the third trial, that is, 20 minutes after injection, for at this point the intensity of the drug's effect reaches its highest in both treatment groups in nearly all phases (see Figs. 9, 10, and 11). A test of significance on running times at phase 1 between the two levels of treatment, 20 minutes after injection, gives $t = 7$ with 8 d.f. significant at the 1% level. However, significance cannot be calculated between the two treatments at phase 2 ($t = 1{\cdot}4$ with 8 d.f.) or at phase 3.

Discussion.—Data have been brought forward to substantiate to some degree the hypothesis posed. It has been possible to demonstrate that the effect of premedication with reserpine measurably alters the course of the LSD-25 disturbance. The data revealed an increase in two types of measures, an increase in intensity over a given period and an increase in the total duration. By and large this increase is in the expected order, namely, the higher the dose of LSD-25 the more profound the effect. Similarly, an ordered relationship has been found along the phase variable, so that the intensity-duration increase decreased over the successive experimental phases.

There is a clear indication that some aspects of the disturbances produced by administration of the LSD-25 are considerably enhanced by premedication with reserpine. Isbell and Logan (1957) recently obtained similar results in experiments conducted with adult male drug addicts serving sentences. His subjects found the combination of drugs, given in the order of 6 mg. reserpine, and, after 22 hours 0·5 μg./kg. LSD-25, considerably more disturbing than when LSD was given exclusively. Isbell utilized a questionnaire technique to assess the intensity of the disturbance.

With these findings in mind it is reasonable to assume that the effects of reserpine pre-treatment somehow alter the intensity-duration of the disturbance induced by LSD-25. It remains then to suggest the possible mechanism which may determine this disturbance. The evidence to date has been discussed in the introduction to this paper. Briefly stated, the assumption made was that reserpine destroys the bonding mechanism required to store 5 HT, thereby releasing it for rapid metabolism (Brodie *et al.*, 1956). It is further suggested that reserpine of itself has no effect on the central nervous system for a period longer than approximately two hours after administration (Sheppard, Lucas, and Tsien, 1955). The reformation of bonding sites takes place over a considerable time span, during which there is a proportionately greater production and turnover of free 5 HT (Udenfriend *et al.*, 1957). If the peripheral effects of LSD-25 in the presence of free 5 HT, *e.g.*, on the excised rat uterus, are also the type of effects the substance has *in vivo*, *i.e.*, in cerebral tissue of the intact rat, then the disturbance produced by LSD-25 will be to some degree proportional to the amount of active 5 HT in the central nervous system. The evidence arising out of the injection of LSD-25 at three distinct points in time during which this reformation of 5 HT bonding sites occurs seems to justify the two following propositions, namely, that an interaction between LSD-25 and 5 HT occurring in the central nervous system appears to be of a similar kind to that found on excised peripheral tissue and that the degree of effect as measured by behavioural indices is relative to a change in 5 HT in the central nervous system. There is very little clarification about the nature of the interaction of LSD-25 and free 5 HT in the central nervous system. Even the most recent findings reported by Woolley and Shaw (1957) have not indicated the direction of the interaction between these two substances. These authors report on experiments conducted on excised human foetal brain cells. Oligodendroglia are cells which are usually regarded as the structural supports to the active neural bodies. Recent findings with time-lapse photography have shown that these cells have a continuous rhythmic pulsating action. Woolley and Shaw have demonstrated that free 5 HT produces tetanic-like seizures of these pulsating cells. On the topic administration of LSD-25 in conjunction with free 5 HT there was some indication that at certain dose levels and varying times of administration, 5 HT activity facilitated and at other levels and times there is an antagonism. This is precisely analogous to the state of affairs in peripheral tissues like the rat uterus. However, as there is little known either about the function of oligodendroglia or the effects of drugs on them there is little point in further speculation now. In Part II the author has pointed out that there is a distinct possibility that 5 HT may be a chemical mediator for the central representation of the autonomic nervous system. In this event the peculiar psychological effects of LSD-25 may be occasioned through its capacity to act as a specific blocking agent to 5 HT or bio-electric inhibitor.

Conclusion

The theory has been current in recent years that the behavioural disturbances produced by LSD-25 are mediated by an antagonism with 5 hydroxytryptamine in the central nervous system. This

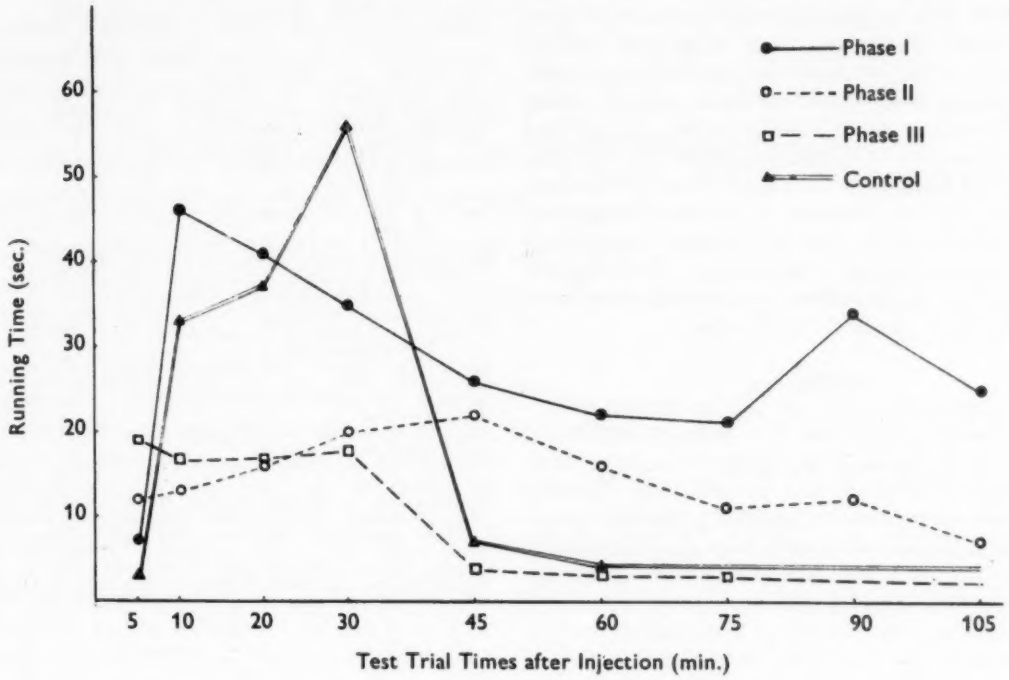

FIG. 12.—Mean running times for treatment after 62·5 μg./kg. LSD-25 after reserpine premedication.

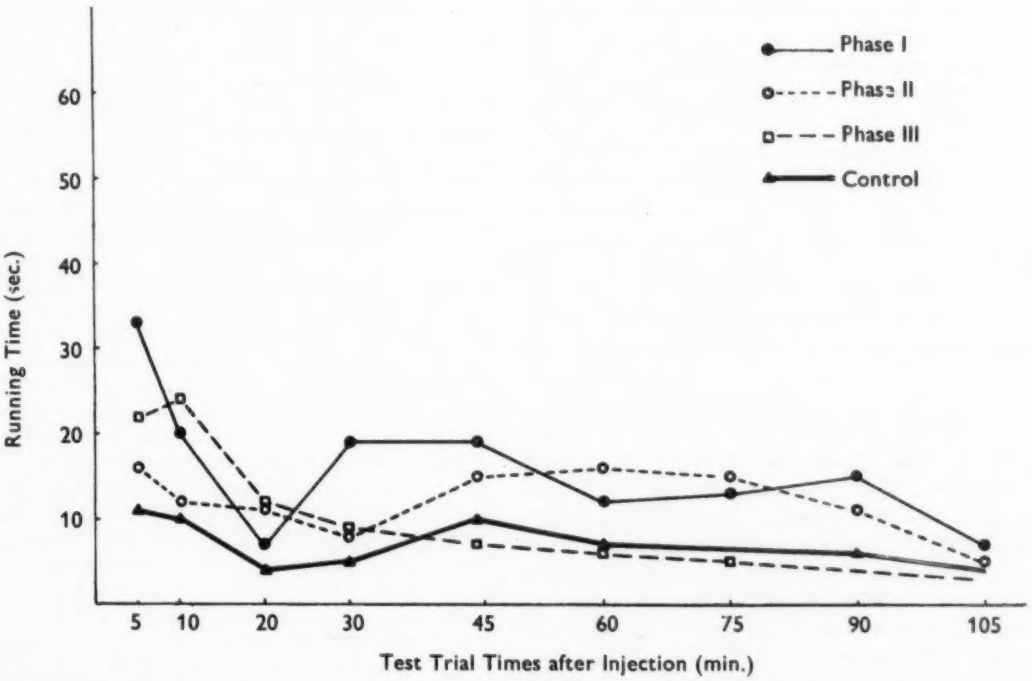

FIG. 13.—Mean running times for treatment after 250 μg./kg. LSD-25 after reserpine premedication.

antagonism can be demonstrated on excised peripheral tissue, but it has been singularly difficult to do the same for the intact central nervous system.

The present experiments go some way in testing this hypothesis by systematically varying the cerebral concentration of 5 hydroxytryptamine *in vivo*. The effect of this treatment is such as to demonstrate that when there is a change in the level of cerebral 5 hydroxytryptamine, the disturbance induced by LSD-25 is considerably augmented. This suggests that the effects of LSD-25 are augmented when there is an increase in cerebral 5 HT activity.

References

Ambache, N. (1955). *Pharmacol. Rev.*, **7**, 467.

Anand, B. K., Dua, S., and Malhotra, C. L. (1957). *Brit. J. Pharmacol.*, **12**, 8.

Bein, H. J. (1956). *Pharmacol. Rev.*, **8**, 435.

Brodie, B. B., and Shore, P. A. (1957). *Ann. N.Y. Acad. Sci.*, **66**, 631.

——, Pletscher, A., and Shore, P. A. (1956). *J. Pharmacal.*, **116**, 9.

Bruce, H. M., and Parkes, A. S. (1949). *J. Hyg. (Lond.)*, **47**, 202.

Burton, A. C., and Edholm, O. G. (1955). *Man in a Cold Environment* (Monographs of the Physiological Society No. 2). Arnold, London.

Erspamer, V. (1956). *Lancet*, **1**, 511.

Glow, P. H. (1957). *Quart. J. exp. Psychol.*, **9**, 206.

Hardisty, R. M., Ingram, G. I. C., and Stacey, R. S. (1956). *Experientia (Basel)*, **12**, 424.

Haverback, B. J., Shore, P. A., Tomich, E. G., and Brodie, B. B. (1956). *Fed. Proc.*, **15**, 434.

Hess, S. M., Shore, P. A., and Brodie, B. B. (1956). *Ibid.*, **15**, 437.

Holzbauer, M., and Vogt, M. (1956). *J. Neurochem.*, **1**, 8.

Isbell, H., and Logan, C. R. (1957). *A.M.A. Arch. Neurol. Psychiat.*, **77**, 350.

Jenkner, F. L., and Ward, A. (1953). *A.M.A. Arch. Neurol. Psychiat.*, **70**, 489.

Kinross-Wright, V. (1955). *Ann. N.Y. Acad. Sci.*, **61**, Art. 1, 174.

Lessin, A. W., and Parkes, M. W. (1957). *Brit. J. Pharmacol.*, **12**, 245.

Paasonen, M. K., and Vogt, M. (1956). *J. Physiol. (Lond.)*, **131**, 617.

Pembrey, M. S. (1895). *J. Physiol. (Lond.)*, **18**, 363.

Rinaldi, F., and Himwich, H. E. (1954). *Amer. J. Physiol.*, **179**, 665.

——, ——, (1955). *Science*, **122**, 198.

Schwartzbaum, J. S. (1955). *Proc. Soc. exp. Biol. (N.Y.)*, **90**, 275.

Sheppard, H., Lucas, R. C., and Tsien, W. H. (1955). *Arch. int. Pharmacodyn.*, **103**, 256.

Shore, P. A., Olin, J. S., and Brodie, B. B. (1957). *Fed. Proc.*, **16**, 335.

Sidman, M. (1956). *Ann. N.Y. Acad. Sci.*, **65**, Art. 4, 282.

Siegel, S. (1956). *Nonparametric Statistics*, p. 119. McGraw-Hill, New York.

Smith, R. P., Wagman, W., Wagman, A., and Riopelle, J. H. (1956). *J. Pharmacol.*, **116**, 53.

Tasher, D. C., and Chermak, M. W. (1955). *Ann. N.Y. Acad. Sci.*, **61**, Art. 1, 108.

Udenfriend, S., Weissbach, H., and Bogdanski, D. F. (1957). In *Hormones, Brain Function, and Behaviour*, p. 147, ed. H. Hoagland. Academic Press, New York.

Welsh, J. H. (1957). University of Oregon Publications, p. 161.

Willberg, M. A. (1914). *Bi. chem. Z.*, **66**, 389.

Woolley, D. W., and Shaw, E. (1954). *Brit. med. J.*, **2**, 122.

——, —— (1957). *Ann. N.Y. Acad. Sci.*, Vol. **66**, Art. 3, p. 649.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 33.

PHYSIOLOGICAL TREMOR IN CHILDREN

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A rhythmic tremor at about 10 c./sec. is a well-known feature of muscular contraction in healthy adults. In some subjects the amplitude of the tremor is such that it is discernible by the naked eye, while in others sensitive methods of recording are required for its detection. While studying this phenomenon Marshall and Walsh (1956) noticed that the tremor in six normal children was slower than that in adults. As this fact has important implications as to the mechanism of the tremor in both children and adults, a more extensive study of physiological tremor in children has been made and is reported here.

Material and Methods

The method which has been used to record the tremor measures acceleration rather than displacement and full details of the technique are given by Marshall and Walsh (1956). Essentially the method consists in the use of an accelerometer double diode valve (Mullard DDR 100) the anodes of which are deflected by acceleration in one plane. Movement of the valve upsets a bridge circuit, and the electrical output is fed through an Ediswan electroencephalographic amplifier to an ink writer. The valve is 9·5 cm. long and 3·3 cm. in diameter; it weighs only 65 g., and can be held comfortably in the palm of the hand.

The child sat in a chair grasping the valve in the palm of the right hand, the limb being maintained by the subject fully outstretched in the pronated position. The tremor recorded was, therefore, that imparted by the whole of the limb musculature and not by a single muscle group. Care was taken that the anodes of the valve were always in the same plane. The child was asked to keep the valve as steady as possible and the recording was then made. The age of the child was noted and in the majority of cases his height was also measured.

The frequency of the tremor was subsequently measured by laying a transparent cursor ruled off in seconds over the tracing and counting the number of waves in a second. Several samples in each record were measured, and difficulty was not encountered by runs of different wave frequencies being present in the records. At the time of making the measurement the observer was not aware of the age or height of the child.

Results

The tremor of 287 children with ages ranging from 2 to 16 years was recorded. The number of children in each age group is shown in Fig. 1. The children comprised a random group attending a Christmas party, and groups from a primary school, a secondary grammar school, and a boarding school. No selection of children was made except to ensure that each age group was adequately represented. It was immediately apparent that in general the tremor is slower in children than the 10 c./sec. seen in normal adults. When the frequency of the tremor is plotted against age it is found that the various frequencies are not evenly scattered throughout the age groups, rather there is a large number of children with tremor at a frequency of 5 or 6 c./sec. (Fig. 1). Children with tremor of this frequency are found in all age groups from 2 years up to 16 years, but the great majority are in the 2-9-year age groups. After 9 years an increasing proportion of children in each age group has a tremor of a higher frequency, until when 16 years is reached it is uncommon to find a frequency of 5 or 6 c./sec. Moreover, the number of children with a tremor of a frequency of 7 or 8 c./sec. is relatively small, suggesting that a fairly abrupt change is made from the 5 or 6 c./sec. rhythm to the adult rhythm of 10 c./sec. Comparing the mean tremor frequency in the 2-9-year age group with that of the 10-16 age group shows the difference to be highly significant ($P<0.001$).

The relationship between age and frequency of tremor is revealed more clearly by plotting the mean frequency for each age group against age as in Fig. 2. This confirms that there is not a simple linear relationship between age and tremor frequency, but that the data can be fitted by two straight lines, one for the 2-9-year age groups and the other for the 10-16 age groups. The difference between the slopes of these two lines is highly significant ($P<0.001$). A considerable number of random observations outside the present series indicates that certainly by the age of 18 years the

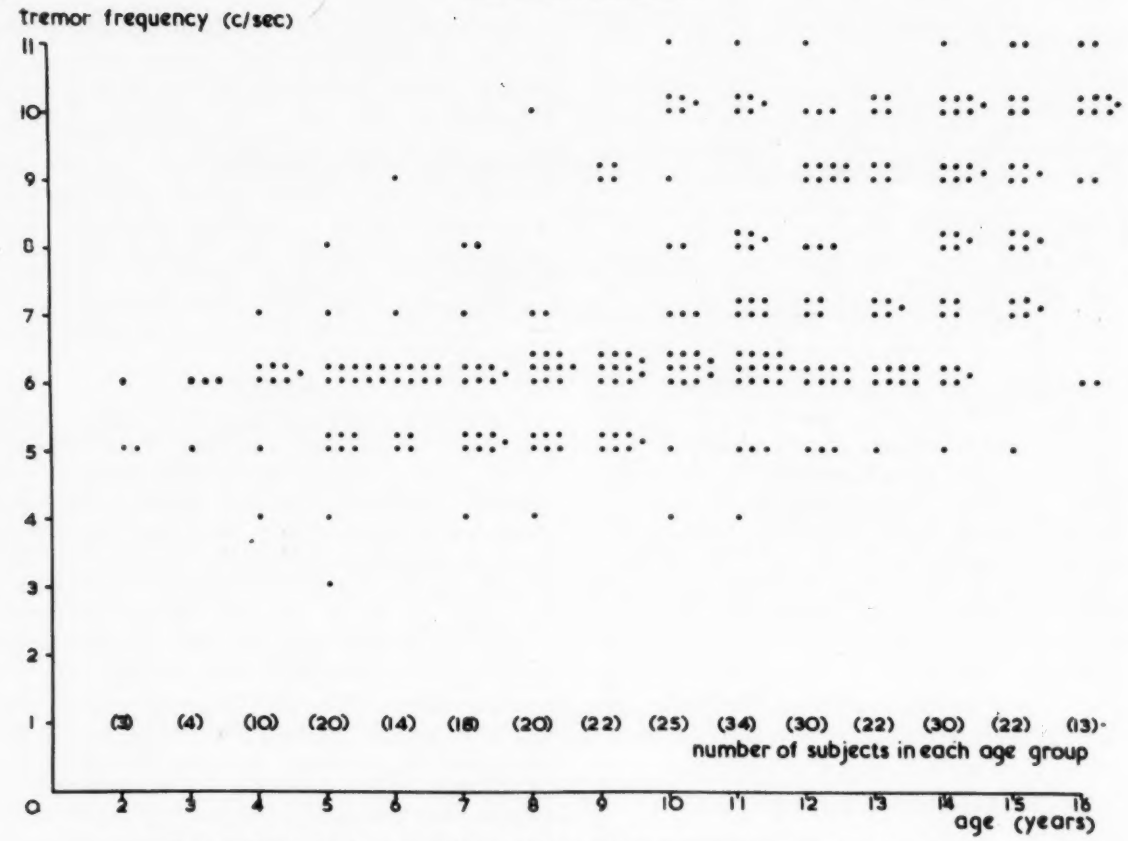

FIG. 1.—Graph showing the number of children with each tremor frequency in each age group.

adult rhythm of 10 c./sec. is established and is maintained throughout the remainder of a healthy life, hence the line if continued beyond the 16-year-old group would become parallel to the abscissa.

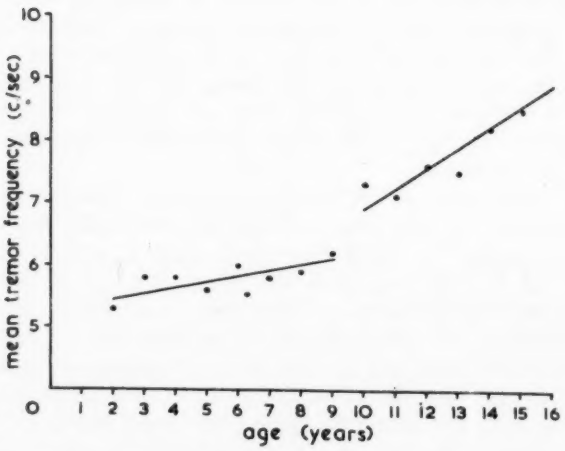

FIG. 2.—Graph showing the abrupt change in the mean tremor frequency for each age group which occurs about the age of 9 years.

The fact that the tremor frequency is not linearly related to age raises the question as to whether tremor frequency is more closely correlated with height than with age, for there is a considerable scatter of height in any age group. The height was therefore measured in 201 of the children over the age span of 5 to 16 years, and ranged from 41 to 73 inches. Plotting frequency against height reveals a less close correlation than between frequency and age. In three age groups (10, 13, and 14 years) the correlation coefficient between height and frequency was calculated and was not significant ($P<0{\cdot}1$).

Discussion

The interest of these observations is largely in the light they throw on the mechanism responsible for physiological tremor. The possibility that the weight of the valve, while trivial for an adult, was sufficient to influence the tremor in children, especially the smaller ones, can be immediately discounted. The valve weighed only 65 g. which is an insignificant weight even for a small child. Moreover, both Marshall and Walsh (1956) and Halliday and Redfearn (1956) have shown that loading a

limb, while increasing the amplitude of the tremor, has no significant influence upon its frequency. The slower tremor in children was not, therefore, due to the relative weight of the valve.

Halliday and Redfearn (1956) suggested that the tremor in adults is due to oscillation round the " servo-loop " from muscle spindle to muscle. They produced evidence (Halliday and Redfearn, 1958) that physiological tremor was lost in some patients with tabes dorsalis in whom there was clinical evidence of interruption of the reflex arcs. It is hard to reconcile the present findings in children with this hypothesis. Conduction velocity in peripheral nerves is proportional to fibre diameter (Cragg and Thomas, 1957). Fibre diameter increases up to about the age of 6 years after which there is no appreciable change; hence it follows that conduction velocity is also stable after this age. As the neural pathways concerned in spinal reflexes increase in length during growth, the reflex time must also increase, and this, in fact, has been shown to occur (Wagman, 1954). Wagman used the latency of the " H reflex " as a measure of reflex time and found, for example, a reflex time of 17 m.sec. at the age of 6 years and one of 23 m.sec. at the age of 9 years. If, therefore, the physiological tremor were dependent on oscillation round the spinal reflex arc, the tremor should be faster in the shorter reflex arc of children than it is in the longer adult reflex arc. The reverse has, in fact, been shown to be the case, hence it is difficult to accept the view that physiological tremor is due to oscillation around the spinal reflex arc.

An alternative consideration is that the 5 or 6 c./sec. tremor found in children is not a slower version of the physiological tremor seen in adults, but is rather a separate phenomenon with its own neural mechanism. It may be that the tremor of childhood is suppressed or replaced by the adult tremor, and this hypothesis would accord with the observation that the distribution of tremor frequencies among the age groups undergoes a fairly abrupt change from the 5 or 6 c./sec. to the 10 c./sec. rhythm. In this regard it is worth pointing out that some pathological tremors have a frequency of about 5 or 6 c./sec. and become apparent as a result of neural structures being damaged by disease. It may be that the 5 or 6 c./sec. tremor of childhood is based on a more primitive neural mechanism, the activity of which is suppressed about the age of 9 years by the development of more adult neural mechanisms. The present evidence does not permit a definite answer to this question but it is clear that mechanisms other than a simple servo-loop must be involved in physiological tremor.

Summary

The tremor of the outstretched hand has been recorded in 287 children. The predominant frequency of the tremor up to the age of 9 years is about 6 c./sec., thereafter the frequency changes fairly abruptly, and by the age of 16 years most children have a tremor frequency of 10 c./sec. The significance of the observations in relation to the mechanism of physiological tremor is discussed.

I wish to thank Mrs. D. Joyce for the statistical analysis and Mr. J. I. MacNaughton for technical assistance.

REFERENCES

Cragg, B. G., and Thomas, P. K. (1957). *J. Physiol. (Lond.)*, **136**, 606
Halliday, A. M., and Redfearn, J. W. T. (1956). *Ibid.*, **134**, 600.
——, —— (1958). *J. Neurol. Neurosurg. Psychiat.*, **21**, 101.
Marshall, J., and Walsh, E. G. (1956). *Ibid.*, **19**, 260.
Wagman, I. H. (1954). *J. Neurophysiol.*, **17**, 66.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 36.

THE MECHANISM OF THE PAIN IN TRIGEMINAL NEURALGIA

BY

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Trigeminal neuralgia (tic douloureux) is characterized by brief paroxysms of pain limited to the facial distribution of the trigeminal nerve and is precipitated by stimuli to sensory endings in the trigeminal receptive area. The condition is relieved by blocking the afferent input of the trigeminal nerve. According to Wyburn-Mason (1953) and Crue, Shelden, Pudentz, and Freshwater (1956), attacks of trigeminal neuralgia can in some cases be abolished by interruption of adjacent cervical nerves.

The neurophysiological mechanism underlying trigeminal neuralgia is still obscure (*cf.* List and Williams, 1957). King and Meagher (1955), King and Barnett (1957), and King, Meagher, and Barnett (1956) described alterations of trigeminal nerve potentials associated with over-reaction to tactile facial stimulation in cats produced by applying alumina gel or strychnine to the spinal trigeminal nucleus. The electrical potential changes in the human trigeminal system associated with the paroxysmal pain, however, remain to be investigated. Moreover, the finding of a correlation between the clinical syndrome of tic douloureux and the electrophysiological phenomena presupposes a detailed knowledge of the clinical events. Since the mechanism of the paroxysmal pain is intimately associated with afferent discharges we have studied with semi-quantitative methods the relation between the attack of pain and stimuli applied to the skin trigger zone. The effect of anti-epileptic drugs, such as hydantoin and lidocain, has also been investigated.

Material and Methods

The present investigation was carried out on 50 patients with trigeminal neuralgia who were admitted to the Neurological Clinic during the years 1946 to 1957 and in whom the attacks could be evoked by mechanical stimulation of the trigeminal receptive area. A necessary requirement was that the patient had an observant mind and was willing to undergo repeated provocations of the attacks.

One patient, an 18-year-old girl, suffered from "symptomatic" trigeminal neuralgia associated with platybasia. In another patient the neuralgia was associated with an intracranial arterial aneurysm. The remainder had the common "cryptogenic" type.

At the beginning of the investigation the attacks were provoked by stroking the trigger zone with the finger tip at, so far as possible, a constant rate, speed, and pressure. Later, a vibratory stimulator was employed, consisting of a pin attached to the membrane of a loud-speaker which led to a Grass stimulator. The head of the pin, which was a round knob, was pressed against the skin. The frequency and amplitude of the vibrations were controlled with the stimulator which was switched on and off manually. The amplitude ranged from 0 to 1 mm. and reached its maximum within 2 m.sec. This provided a comparatively well-defined and reproducible mechanical stimulus of the skin.

Results

Some patients have, during particularly severe periods of the disease, attacks of pain which apparently start spontaneously. They occur without tangible external irritation, such as touching the face, talking, or eating, which is usually necessary for precipitating an attack during less active periods. The same patients may have periods of remission when not even external stimuli will provoke an attack. It is also a well-known fact that the severity of the disease can vary from day to day or from hour to hour.

Since even in patients with "spontaneous" attacks the pain is relieved by blocking the afferent pathway of the fifth nerve, it may be assumed that the pain is precipitated by afferent discharges and that deterioration or improvement reflects a lowering or raising of the attack threshold. During periods of "spontaneous" attacks a minimum stream of afferent impulses in the trigeminal nerve is evidently sufficient to provoke an attack. During periods of improvement a higher intensity of afferent impulses is required, and during periods of remission the threshold is not reached even with a high intensity of afferent discharge.

The rapid fluctuation in the severity of the symptoms indicates that the neurophysiological state responsible for the tic syndrome is very unstable. Accordingly the quantitative relationship

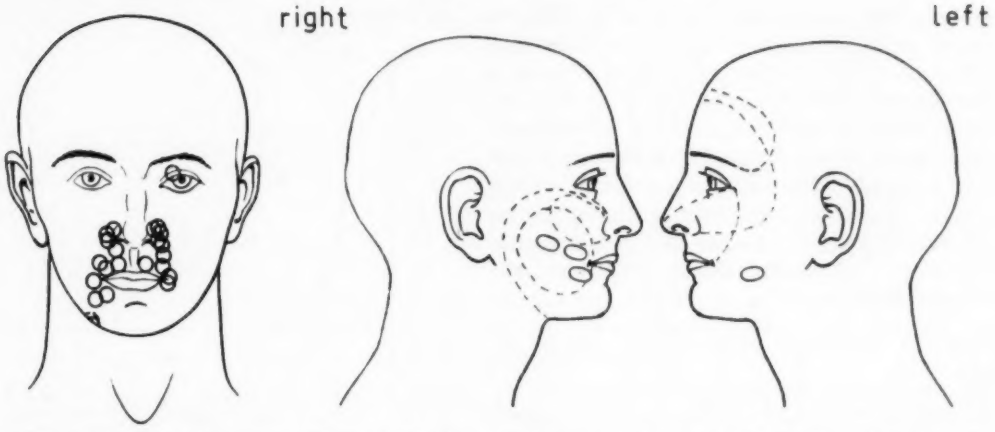

FIG. 1.—Distribution of 31 trigger zones in 30 patients. Circles denote circumscribed and broken lines widespread, cutaneous trigger zones. Ovals indicate localization to alveolar gingiva.

between the paroxysmal pain and the afferent discharge may be expected to vary not only in different individuals but also in the same individual at different examinations as well as during the course of a prolonged examination. A basic pattern of the trigger mechanism, however, may be distinguished.

The Trigger Zone.—The site of the trigger zone in the last 30 patients examined is shown in Fig. 1. Although the trigger zone could be located almost anywhere within the trigeminal receptive area it was most common in the nasolabial fold, on the upper lip, the lateral part of the lower lip, and the alveolar gingiva. Some patients had two trigger zones and some reported that their trigger zone had shifted from one point to another during the course of the disease. One patient stated that she had a trigger zone outside the trigeminal area, located in the ipsilateral axilla. At the time of examination, however, it was not present, and therefore the information is uncertain. Crue *et al.* (1956) reported a case of trigeminal neuralgia with a trigger zone on the big toe.

In some of the patients the trigger zone was large and diffuse but in the majority it was comparatively small and well-defined. How small the trigger zone can actually be is difficult to determine, but in some of our patients it was not larger than 1 or 2 sq. mm. There was no obvious relationship between the severity of the attack and the size of the trigger zone. Very severe attacks could be fired in patients with an almost punctate trigger zone as well as in those with a large trigger zone. The pain usually started near the trigger zone. Although it was rather difficult for the patients to determine accurately the exact spot in which the pain actually started, it was obvious that the pain did not always start in the trigger zone. For example, in one patient with the trigger zone on the upper eyelid the pain started in the cheek (*cf.* List and Williams, 1957).

Adequate Stimulus.—It is common knowledge that the attacks of pain are precipitated by tactile stimulation of the trigger zone (*e.g.*, touching the face, as in shaving or washing) or by stimuli such as talking and mastication which increase the proprioceptive inflow. Pain is a less effective stimulus. In our patients severe pinching of the skin of the trigger zone with forceps failed to evoke an attack. Thermal stimuli (a warm metal rod or cube of ice) were ineffective when applied slowly, as was slowly-applied firm pressure. On the other hand, sudden application or release (off-effect) of pressure evoked an attack in susceptible individuals. This suggests fairly rapid adaptation of the receptors responsible for the paroxysmal pain. Stroking the skin with a blunt object, *e.g.*, the finger of the examiner, was a highly effective stimulus. Firm stroking is perceived as touch, light stroking as touch and tickle. Rapid displacement of a few hairs may also be effective. This is perceived as a tickle, with or without the component of touch. Slow displacement of the hair, however, or even a slow, steady, painful pull on the hair failed to fire an attack. The vibratory stimulus, causing a rapid distortion of the skin, was effective in susceptible individuals.

Electrical stimulation was employed in an effort to determine which fibres convey the effective impulses. In two patients with the trigger zone on the upper lip a needle electrode was inserted into the infraorbital foramen. Repetitive weak shock stimuli to the maxillary nerve gave rise to the vibratory sensation typical of tactile fibre stimulation (*cf.* Kugelberg, 1944), but did not evoke a paroxysm of pain. An increase of the stimulus strength to

threshold for the larger pain fibres still failed to provoke an attack. These results indicate either that the fibres responsible for the paroxysmal pain have a smaller diameter and a higher threshold than the large pain fibres or possibly that the spatial and temporal pattern of the triggering discharge is too specific to be imitated by electrical shock stimulation of the nerve. Shock stimulation did not appear to have an inhibitory action since the attack could still be triggered from the upper lip during the electrical stimulation.

Eliciting the Attack of Pain.—Four factors are discussed.

(1) *Minimal Afferent Discharge.*—In three patients it was possible to trigger an attack by rapid displacement of a single hair. In susceptible individuals evidently only a minimum number of nerve fibres are required to convey impulses to the critical structure to fire an attack. This does not, however, imply that these were the only fibres responsible for the attack. A proper background discharge is probably also necessary.

(2) *Spatial and Temporal Summation.*—Provided the trigger zone was not too small, it was possible to show that spatial summation of impulses from a larger area triggers the paroxysm of pain at a lower stimulus strength and at a shorter latency than if a small area is stimulated. In susceptible individuals however, a larger spatial summation does not seem to be a prerequisite for evoking an attack. As mentioned earlier, displacement of a single hair was sometimes sufficient to evoke an attack.

A temporal summation of impulses was evident in all but a few of the patients. In one of these displacement of a few hairs of the nostril by a single pulse of the vibrator evoked a stab of pain, which was accompanied by a twitch of the face with a latency of 57 m.sec. (Fig. 2). In a few patients a single touch of the trigger zone similarly elicited a stab of pain with a very short latency. Since the patients did not react with a well-defined twitch

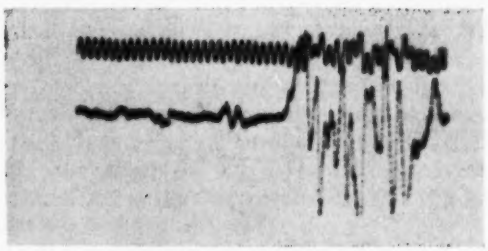

FIG. 2.—Electromyogram from the orbicularis oris. Latency of facial twitch accompanying a stab of pain evoked by a sudden displacement of hairs of the nostril. The stimulus started the cathode ray sweep. Time: 500 c./sec.

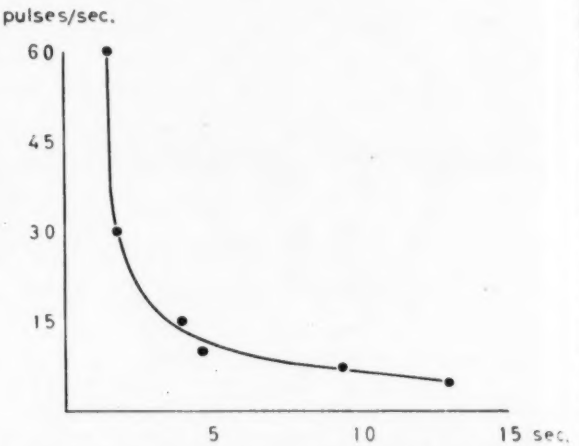

FIG. 3.—Summation time (abscissa) in relation to vibration frequency (ordinate).

of the face it was not possible to measure the latency time accurately.

In the majority of the patients, however, it was necessary to continue the stimulation for a longer period in order to elicit pain. The length of the period was largely dependent on the stimulus intensity. A typical example is shown in Fig. 3. Vibratory stimuli at the rate of 7 per second evoked an attack after a summation time of 15 sec. By increasing the frequency to 30 vibrations per second the summation time was gradually reduced to about 1·5 sec. Further increase in frequency did not further reduce the latency time. Variations solely in the amplitude of the stimuli had the same effect on the latency. A summation time up to 30 sec. was observed with weak stimulation.

The results indicate that the excitatory state necessary to fire an attack may be built up over a considerable time by temporal summation of afferent impulses.

One may ask how quickly the effect of the stimulus subsides. To test this the trigger threshold was determined at different intervals after a conditioning stimulus. The minimum duration of a stimulus which fires a brief jab of pain was estimated. A test stimulus of equal intensity was delivered 5, 10, 15, or 25 seconds after the conditioning stimulus and the duration necessary to reach the trigger threshold was measured. The quotient of the duration of the test stimulus and the conditioning stimulus is plotted against the stimulus interval in Fig. 4. Each point in the figure is the mean of three or four pairs of measurements.

The raised excitability evidently falls rather sharply after cessation of the stimulus but may remain above the resting value for 20 to 25 sec. The raised excitability in this experiment was not due

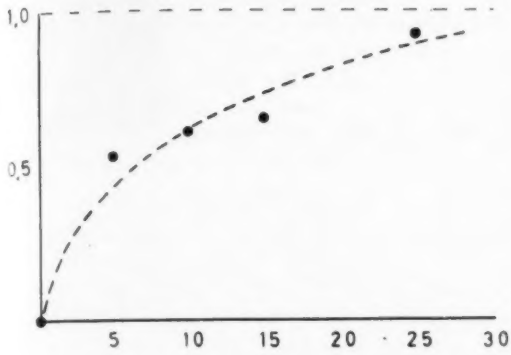

FIG. 4.—Decay of excitability following a conditioning skin stimulus to the trigger area. The quotient of the duration of the test stimulus and the conditioning stimulus (ordinate) is plotted against the stimulus interval (abscissa).

to the jab of pain since the same result was obtained if the conditioning stimulus was just subthreshold for triggering the pain. Experiments of this type are difficult and can be performed only in subjects with a stable trigger threshold. The result was consistent in three out of five patients tested.

(3) *Effect of Stimulation.*—Stimulation of the trigger area in our patients resulted in: (*a*) Paraesthesia in the form of pins and needles or tingling (this was uncommon); (*b*) a jab of pain which may recur in rapid succession when the stimulation is continued; (*c*) sustained pain which continues when the stimulus is prolonged but does not outlast the stimulus; (*d*) sustained pain which continues even after the stimulus is discontinued.

More than one type may occur in one and the same individual although one type usually predominates. During periods of improvement the response in (*d*) may often be supplanted by the (*c*) type.

The pain reaches its maximal intensity rapidly, usually within a few seconds, remains stable for a variable period, and then gradually subsides. Alterations in the intensity are accompanied by variations in the spatial distribution of the pain. The pain spreads rapidly at the beginning of the attack but recedes more slowly at the end of the attack, generally in the reversed order of its evolution. Some patients complain of tenderness to pressure in the painful area during an attack that is not severe enough to mask the tenderness. In our patients the attacks seldom lasted longer than two to three minutes.

(4). *Refractory Period.*—All clinicians who have treated a large number of patients with trigeminal neuralgia will have encountered those who relate that immediately after an attack they can safely go on eating and talking for a while without running the risk of a new attack. This, of course, indicates that a refractory period follows the attack. The time relations, however, do not appear to have been investigated.

The patient, E. J., had, before trigeminal rhizotomy, during the course of one day's observation, spontaneous attacks of severe pain of 30 to 60 sec. duration at fairly regular intervals, with free intervals of one and a half to two and a half minutes' duration (Fig. 5, upper diagram). Since the paroxysms presumably were evoked by a more or less continuous stream of minimal afferent discharges in the trigeminal nerve, the intermittent response to continuous stimulation is presumptive evidence of a refractory phase. To test this, the intensity of the afferent discharge was increased by a series of light strokes applied with the finger-tip to the trigger zone on the patient's cheek at the rate of three strokes per second. This reduced the interval between the attacks to about 50 seconds (Fig. 5, middle diagram). If, in

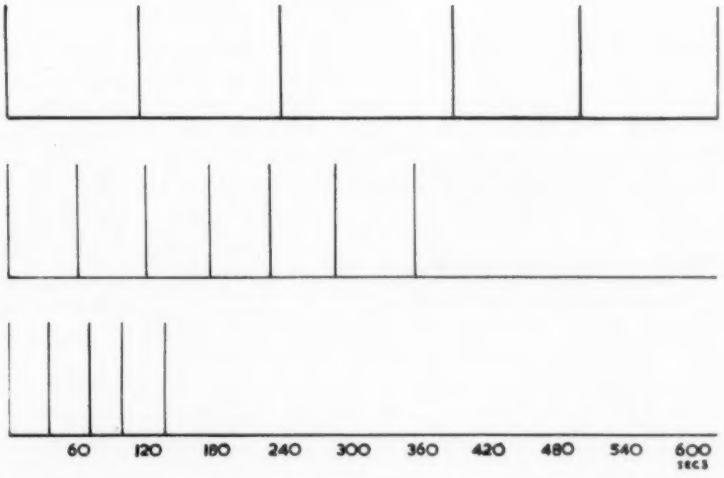

FIG. 5.—Duration of the free interval between attacks. *Upper diagram*, in a series of spontaneous attacks; *middle diagram*, attacks provoked by continuous stroking of the trigger area at the rate of 3 per sec.; *lower diagram*, stroking at the rate of 6 per second.

FIG. 6.—Refractory phase of a pain paroxysm tested by stroking the trigger area intermittently for periods of 10 sec. Filled in area denotes attacks, vertical lines a stab of pain. The interrupted line below the base line represents 10-second periods of stimulation.

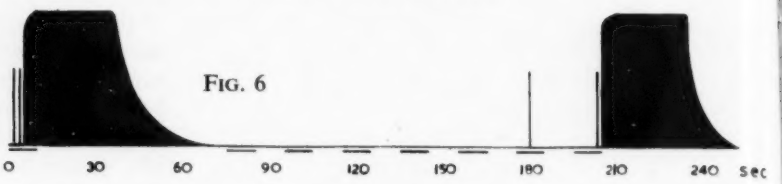

FIG. 6

order further to increase the afferent discharge, the strokes were applied at the rate of six per second, the free intervals were reduced to about 30 seconds (Fig. 5, lower diagram). Further increase in the intensity of the afferent discharge by strokes applied at a maximal speed and frequency reduced the free interval but little. It could not be reduced to less than 20 seconds, and the attacks continued to come rhythmically during all forms of stimulation.

If the threshold for eliciting an attack which follows an antecedent attack is tested by a more intermittent stimulation, a similar condition is found, as exemplified in the patient H. S. This patient had no spontaneous paroxysms but light stroking of the chin at the rate of three strokes per second for a period of 10 seconds regularly elicited a very severe attack of pain of about two minutes' duration. If the stroking was repeated at 20-second intervals after an antecedent attack, the next attack was evoked first after about two minutes (Fig. 6). To reduce the interval between the attacks required intensification of the stimulus. Here also it was not possible to reduce the free interval to less than 20 seconds. The result was the same if only one 10-second period of stimulation was interpolated after each antecedent attack but at varied intervals.

From these examples it is clear that the attacks of pain are followed by a refractory phase during which the threshold is raised. At first the refractory phase is absolute for the stimuli tested and excitability returns gradually to its former level two to three minutes after the end of a severe attack.

Furthermore, the attack following within the refractory phase of an antecedent attack tends to be diminished in duration and intensity and shows, possibly, less tendency to spread. This is exemplified in the patient E. K., who periodically had severe attacks at irregular intervals. Fig. 7 shows the duration of the individual "spontaneous" attacks

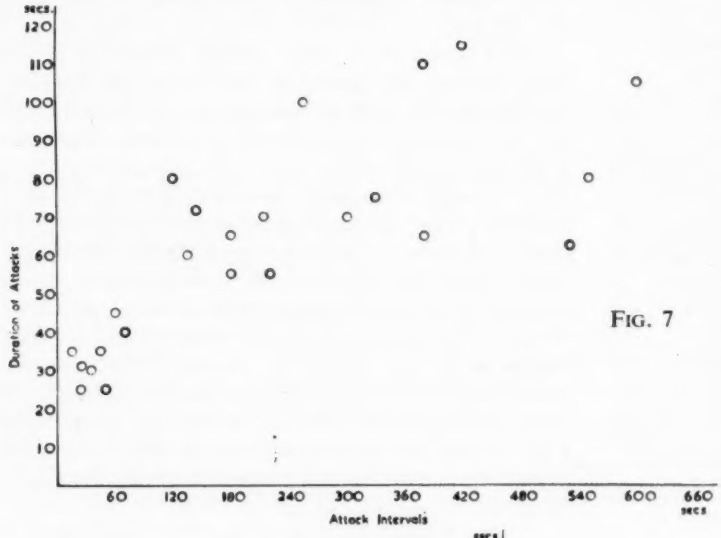

FIG. 7

FIG. 7.—Spontaneous attacks. Attacks which occur within two minutes after an antecedent attack have a shorter duration than those occurring after a longer free interval.

FIG. 8.—A series of attacks evoked at various intervals showing decrease in duration of attack with decrease in free interval.

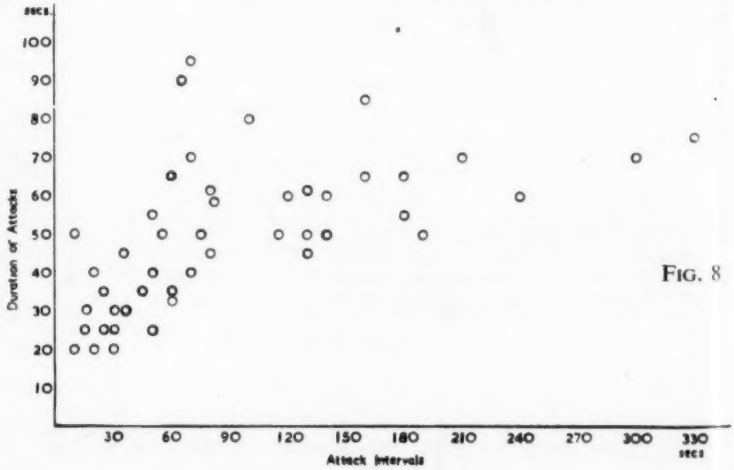

FIG. 8

plotted against the duration of the free interval which preceded the attack. If the free interval was less than two to three minutes, the paroxysm decreased in duration with decrease in length of free interval. This was also the case if, when the patient had no spontaneous attacks, a test attack was interpolated at varied intervals after a similarly provoked antecedent attack (Fig. 8). Moreover, it was again observed that no spontaneous paroxysms occurred at intervals of less than 20 seconds, nor was it possible to evoke them earlier (Fig. 6-8).

In paroxysms occurring within the refractory phase after an antecedent attack, diminution in the intensity of the pain is not so obvious as the decrease in the duration of the paroxysm. Some patients admit a considerable decrease in the intensity of the pain while others do not. It is possible that the discharge of pain impulses during the paroxysm is so intense that discrimination is lost.

It is desirable at this point to establish that the refractory phase is dependent chiefly on the attack of pain and not on the stimulus that precipitates it. With the rough methods of evaluation used here no refractory phase could be detected after a series of stimuli to the skin for periods of 10 seconds to two minutes at an intensity just below threshold. Nor did a stimulus of 60 to 70 seconds' duration applied at the beginning of the refractory period alter the rhythm of the attacks occurring spontaneously at regular intervals. The intensity of the stimulus used was sufficiently strong to provoke an attack at the end of the refractory period.

The duration of the refractory phase is a function of the duration as well as of the intensity of the preceding attack. Attacks of a few seconds' duration show hardly any refractoriness as tested by the vibrator. Furthermore, in two patients who had paroxysms of only slight pain, it was possible, by stimulation of the trigger area, to maintain an attack for 19 minutes during which time no absolute refractory period occurred. The pain, however, steadily decreased in intensity during the attack and was finally replaced by a sensation of glowing warmth. Conversely, the duration of the refractory phase could be increased by provoking a series of attacks in rapid succession. Although in this case the duration of the attacks decreases and consequently the duration of the refractory period, the sum effect of the series may be an increase.

In the patient E. K., who at one time had fairly regular spontaneous attacks, each series of provoked attacks was followed by a compensatory pause.

Effect of Anti-epileptic Drugs.—Of the different drugs used therapeutically, novocaine has been reported to be effective not only when given as a local anaesthetic for blocking conduction in the peripheral trigeminal pathway, but also when injected into the systemic circulation in comparatively small doses (see Kubànyi, 1956).

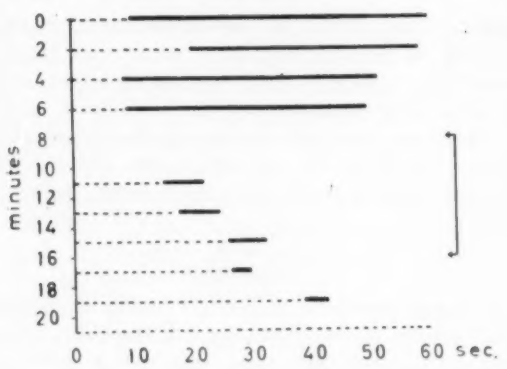

FIG. 9.—Increase in summation time (broken line) and decrease in duration of pain (thick solid line) following intravenous injection of lidocaine (between arrows), 2 mg./kg. Vibratory stimulation at two-minute intervals before (time 0-6) and after (time 11-21) the beginning of the injection.

In the present investigation lidocaine was given intravenously to six patients and its effect tested by vibratory stimulation of the trigger area at regular intervals which were longer than the refractory period. In all six patients lidocaine, in a dose of 2 to 4 mg./kg. body weight, resulted in partial or complete relief of the pain paroxysms. Fig. 9 illustrates a typical result obtained in the patient N. L., in whom attacks could regularly be evoked before the injection. It is seen that during the course of the injection the summation time increases and the duration of the pain paroxysm decreases until complete abolition is obtained. Owing to the rapid elimination of the drug (Sung and Truant, 1954), however, the effect is only temporary and the attacks usually regained their original intensity one hour after the injection.

Several workers have found that diphenylhydantoin given orally is of benefit in the treatment of trigeminal neuralgia (see Kubànyi, 1956; Berczeller and Szecsödy, 1956). In the present series five patients were given intravenous diphenylhydantoin (" epanutin ": Parke Davis) in a dose of 3 to 5 mg./kg. The results were about the same as with lidocaine, although the number of patients is too small to permit a detailed comparison. The total relief of pain obtained with intravenous diphenylhydantoin was short-lived, but the patients stated that the attacks were less intense and less frequent during the rest of the day. Four of these patients were also given barbiturates. A solution of diemal and allypropymal (" hypnofen ": ACO) was given

intravenously until the patient became drowsy, *i.e.*, a dose of 5 to 10 mg./kg. As a rule attacks of maximum intensity and duration could still be elicited after the injection.

Thus the results obtained in acute experiments and controlled by measurements of the trigger threshold confirm the clinical observations reported earlier.

Discussion

The adequate stimulus for eliciting an attack of pain seems to be distortion of the hair, skin, or mucosa. Our observations indicate a fairly rapid adaptation of the critical receptors engaged by such stimuli. Since pain and thermal stimuli were largely ineffective it may be concluded that the afferent discharge which triggers the pain arises from receptors responding to touch.

However, it must be borne in mind that touch stimuli give rise not only to a sensation of touch but also to a sensation of tickle. In fact, the threshold for tickle is lower than that for touch and even if a firm touch is not perceived as tickle it is clear that afferent discharges from receptors responsible for tickle must be evoked. There is no general agreement on the relationship between the tickle sensation and the touch or pain sensation (Graham, Goodell, and Wolff, 1951). These authors consider that tickle is mediated by the same nerve fibres as itch and pain. It seems to be established that the tickling sensation in the trigeminal area is subserved by fibres entering the spinal V tract and nucleus, since it is abolished by trigeminal tractotomy which leaves the components of touch more or less intact (Zotterman, 1939). Our experiments do not exclude the possibility that the receptors responsible for tickle play an important role in initiating the pain paroxysm.

The negative results of electrical stimulation suggest that the effective impulses are not transmitted by the largest touch fibres.

As shown by Zotterman (1939) in his fundamental studies on the cat, a light touch evokes action potentials in delta fibres, usually followed by action potentials of still slower fibres, probably belonging to the C group, *i.e.*, fibres earlier considered to subserve pain. A firm touch engages fibres from the largest down to the smallest. Douglas and Ritchie (1957) have confirmed with another technique the findings of Zotterman. Indeed these authors consider that the bulk of delta and unmyelinated fibres mediate touch rather than temperature and pain. Thus it may be concluded that the fibres engaged by touch stimuli have a broad calibre spectrum. It is believed that the largest fibres of the trigeminal nerve chiefly go to the main sensory nucleus and the delta (*cf.* Sjöqvist, 1938) and unmyelinated fibres to the spinal tract nucleus. Thus a skin stimulus that evokes pain paroxysms feeds impulses not only into the main nucleus but to a large extent also to the spinal nucleus.

The summation time and the duration of the attacks varied considerably in our series. Whether there is a qualitative or merely a quantitative difference in the mechanisms underlying the short latency jab of pain and the attacks that requires a long summation time is not clear.

The short latency jab of pain may possibly be explained by a simple interaction or short circuiting of, for example, the touch and pain fibres. Animal experiments have shown that such an artificial synapse has a delay that is exceedingly short (Arvanitaki, 1942; Granit and Skoglund, 1945; Skoglund, 1945). In one of our patients, the motor response to skin stimulation which evoked a pain paroxysm had a latency of about 60 m.sec. The bilateral distortion of the face resembled a startle response which in fact has a similar latency. Thus, if the twitch were the result of the pain, the latter must have very short latency.

In most cases, however, a more or less long-lasting attack was fired after a considerably longer summation time. A summation time of 15 to 30 seconds was not uncommon. It is highly probable that the summation takes place in the structure responsible for the attack rather than in the receptors. The characteristic refractory period of up to two to three minutes after an attack is scarcely the result of a refractory phase in the receptors since it was shown to be a function of the intensity and duration of the attack and independent of skin stimuli strong enough to discharge the receptors. It would seem that an excitatory state is gradually built up by a temporal and spatial summation of afferent impulses and when it reaches a critical level the attack is fired. This process would be expected to be accompanied by a slow potential change. A slow change does not fit in with the properties of an artificial synapse between nerve fibres nor has a similar phenomenon been reported from pathological ganglia in animal experiments, although the latter has admittedly been little investigated. It is, however, of the type encountered in central structures.

Once an attack is fired it frequently outlasts the stimulus which initiated it. The stimulus itself does not have such a long-lasting effect, since it was shown that the excitability, as reflected by the trigger threshold, diminishes fairly rapidly after the stimulus is withdrawn. The cause of the prolonged maintained discharge would therefore be an event that is started by the attack. This event is a strong

excitant since it may keep a very strong pain alive for one to two minutes and when it has lost its potency skin stimuli, no matter how strong, often cannot revive the attack.

The refractory phase is certainly intimately associated with the paroxysmal character of the pain and responsible for the cutting short of the attack. Here again slow changes are encountered in the excitability of the mechanism underlying the pain.

The pathologically altered structure that is responsible for the trigeminal neuralgic syndrome is most likely located in the brain-stem, as also was thought by Crue *et al.* (1956) and List and Williams (1957). A thalamic origin of trigeminal neuralgia as proposed by Lewy and Grant (1938) seems unlikely since it is improbable that a lesion at this level could account for such a spatially limited pain phenomenon. The interesting observations of King *et al.* (1955, 1956, 1957) in animal experiments are at present difficult to apply to the phenomena we have studied since the potential changes in the cat proceed on a time scale in milliseconds as compared to seconds and minutes in man.

The fact that anti-epileptic drugs, such as hydantoin and lidocaine (cf. Bernhard and Bohon, 1955; Bernhard, Bohon, and Höjeberg, 1955), raise the trigger threshold for the pain favours the theory of a central origin. In fact Trousseau has already designated tic douloureux "neuralgia epileptiforme". It does not, however, prove a central origin of the pain since both drugs also act on peripheral nerves (Bernhard and Valleala, 1958; Morrell, Bradley, and Ptashne, 1958).

If it is correct that the origin of the pain in most cases of trigeminal neuralgia is located centrally the favourable effect of Taarnhøj's (1952) operation seems to be explained by a blocking of critical fibres and a resultant reduction of the afferent discharge essential for eliciting the pain paroxysm.

Summary

An investigation has been made in 50 patients with trigeminal neuralgia of the relationship between stimuli applied to the trigger zone and the pain paroxysm. The results are as follows:—

The adequate stimulus for precipitating an attack is touch and possibly tickle, rather than pain or temperature. There is evidence that the largest touch fibres are not involved. This is discussed in relation to the fact that the fibres engaged by touch stimulus have a broad calibre spectrum and therefore feed impulses not only into the main trigeminal nucleus but also to a large extent into the spinal V nucleus.

Rapid displacement of a single hair was sometimes sufficient to provoke an attack but in most cases a larger spatial summation of afferent impulses was necessary.

A temporal summation of impulses over a considerable time was in the majority of cases necessary to trigger an attack. Summation times of 15 to 30 seconds were often observed, provided the stimulus was weak. In some cases, however, the summation time was short.

Cessation of the stimulus is followed by a rapid fall in excitability, although it may remain above resting value for up to 20 seconds after the stimulus, as seen in three patients.

The attack is followed by a refractory period of up to two to three minutes, depending upon the duration and intensity of the pain. Attacks which occur within the refractory phase of an antecedent attack tend to be shorter.

Anti-epileptic drugs, such as lidocaine and hydantoin, were found to raise the attack threshold as well as to shorten the duration of the attack by diminishing its tendency to self-maintenance.

The long summation times, the tendency of the attack to be self-maintained, the effect of anti-epileptic drugs as well as the long-lasting refractory period, suggest that the mechanism responsible for the paroxysmal pain is situated centrally, probably in the brain-stem in structures related to the spinal V nucleus.

References

Arvanitaki, A. (1942). *J. Neurophysiol.*, **5**, 89.
Berczeller, E., and Szecsödy, E. (1956). *Nervenarzt*, **27**, 369.
Bernhard, C. G., and Valleala, P. (1958). *Exp. Cell. Res.*, Suppl. 5, 201.
——, and Bohon, E. (1955). *Brit. J. Pharmacol.*, **10**, 288.
——, ——, and Höjeberg, S. (1955). *Arch. Neurol. Psychiat.*, **74**, 208.
Crue, B. L., Shelden, C. H., Pudenz, R. H., and Freshwater, D. B. (1956). *Neurology*, **6**, 196.
Douglas, W. W., and Ritchie, J. M. (1957). *J. Physiol. (Lond.)*, **139**, 385.
Graham, D. T., Goodell, H., and Wolff, H. G. (1951). *J. clin. Invest.*, **30**, 37.
Granit, R., and Skoglund, C. R. (1945). *J. Physiol. (Lond.)*, **103**, 435.
King, R. B., and Barnett, J. C. (1957). *J. Neurosurg.*, **14**, 617.
——, and Meagher, J. N. (1955). *Ibid.*, **12**, 393.
——, ——, and Barnett, J. C. (1956). *Ibid.*, **13**, 176.
Kubányi, E. (1956). *Trigeminusneuralgie*. Urban & Schwarzenberg, Vienna.
Kugelberg, E. (1944). *Acta physiol. scand.*, **8**, Suppl. XXIV.
Lewy, F. H., and Grant, F. C. (1938). *Arch. Neurol. Psychiat. (Chicago)*, **40**, 1126.
List, C. F., and Williams, J. R. (1957). *A.M.A. Arch. Neurol. Psychiat.*, **77**, 36.
Morrell, F., Bradley, W., and Ptashne, M. (1958). *Neurology*, **8**, 140.
Sjöqvist, O. (1938). *Acta psychiat. (Koh.)*, Suppl. XVII, 139.
Skoglund, C. R. (1945). *J. Neurophysiol.*, **8**, 365.
Sung, C. J., and Truant, A. P. (1954). *J. Pharmacol. exp. Ther.*, **112**, 432.
Taarnhøj, P. (1952). *J. Neurosurg.*, **9**, 288.
Wyburn-Mason, R. (1953). *Brit. med. J.*, **2**, 119.
Zotterman, Y. (1939). *J. Physiol. (Lond.)*, **95**, 1.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 44.

LUMBOSACRAL SPINA BIFIDA CYSTICA WITH CRANIOVERTEBRAL ANOMALIES: REPORT OF TWO CASES PRESENTING WITH NEUROLOGICAL DISORDER IN ADULT LIFE

BY

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Neurological disorders associated with spina bifida are usually either present at birth or arise in early life. There are two main types. First, lesions of the cauda equina; secondly, lesions at the foramen magnum. Occasionally, symptoms do not make their appearance until adult life and then the developmental nature of the disorder may not be recognized. We propose to give an account of two patients with both lumbosacral spina bifida cystica and craniovertebral anomalies who developed a neurological disorder in adult life as a result of lesions of the cerebellum and brain-stem respectively. We are not aware of any previous record of this association.

Case Reports

Case 1.—G. B. L., aged 34 years, a carpenter and joiner, was admitted to the Cardiff Royal Infirmary on August 9, 1956, for investigation of his complaint of weakness of the legs of one year's duration. He was born with a lumbosacral meningomyelocele (Fig. 1) and wore a protective truss. He did not suffer from enuresis and his only complaint had been of transient sensations of weakness and numbness of the legs whenever he accidentally compressed the meningocele. Sometimes he experienced occipital headache and discomfort if he slept in a supine position.

Difficulty in walking was first noticed one year previously. The left foot, and, shortly afterwards, the right foot began to drag and he frequently stumbled or tripped over kerbs, steps, or on uneven surfaces. Paraesthesia was present in both feet and as weakness of the legs progressed he found his sense of balance was also deteriorating. Nevertheless, he was able to ride a bicycle until two months before admission and he continued at his work. In the last month he could only ascend stairs with much effort and he had begun to feel " pins and needles " in the fingers of each hand. He had no complaints referable to the cranial nerves and sphincter function remained normal.

Examination.—His general condition was good and body configuration was normal. His neck was not short. Gait was slow and laboured; he shuffled along, stumbled when he turned, and swayed when he closed his eyes. The only abnormality in the cranial nerves consisted of fine horizontal nystagmus on right and left lateral gaze. There was no spontaneous nystagmus or oscillopsia and the fundi were normal. The jaw jerk was normal; speech was normal and there were no bulbar signs.

The range of neck movements was normal but he disliked fully extending his head because of vertigo. Power in the arms was normal, and there was no wasting, incoordination, or sensory impairment. The arm reflexes, however, were abnormal. Both biceps and radial reflexes were absent; the triceps jerks were exaggerated. There was brisk finger flexion on attempts to elicit biceps and radial reflexes.

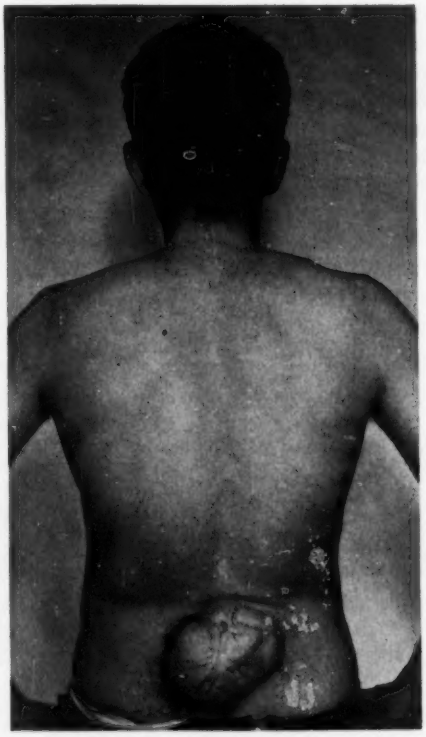

FIG. 1.—Case 1: Lumbosacral meningomyelocele.

FIG. 2

FIG. 2.—Case 1: Radiograph of lumbosacral spine; spina bifida L3 to S1.

FIG. 3.—Case 1: Radiograph of base of the skull, showing gross enlargement of the foramen magnum.

FIG. 4.—Case 1: Upper cervical laminectomy showing protrusion of right cerebellar tonsil through the foramen magnum. Note the tortuous venous plexus.

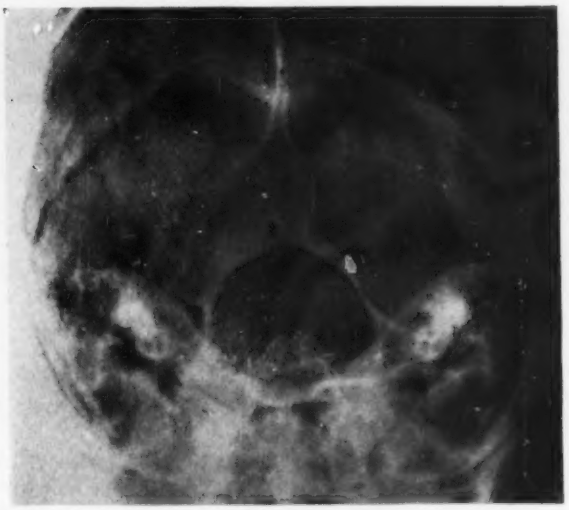

FIG. 3

There was moderate weakness of both lower limbs especially of hip flexion; dorsiflexion of the feet was normal. There was no wasting and muscular development of the legs was good. Both knee jerks were much exaggerated; the left ankle jerk was reduced and the right was absent. Both plantar reflexes were extensor. There was a slight degree of clawing deformity of the right foot. Superficial sensation in both lower limbs to mid-thigh level was impaired. Appreciation of passive movements of the great toe was defective and vibration sensation was considerably impaired at the shins.

Radiological Examination.—In the lumbosacral spine posterior spina bifida from L3 to S1 (Fig. 2) was seen.

The foramen magnum (Fig. 3) was grossly enlarged (antero-posterior diameter 5 cm., transverse diameter 5·5 cm.). There was no evidence of hydrocephalus, chronic intracranial hypertension, or basilar impression.

An anterior view of the cervical spine showed partial posterior spina bifida of C2, C5, and C6. A lateral view showed enlargement of the antero-posterior diameter of the upper cervical spinal canal. Measurements were: C1, 27 mm.; C2, 25 mm.; C3, 17 mm.; C4, 16 mm. Average normal readings are: C1, 22 mm.; C2, 20 mm.; C3, 17 mm.; C4, 16 mm.

Lumbar puncture yielded a clear spinal fluid with a protein content of 90 mg. %, and a slow rise and fall of fluid on jugular vein compression.

Opaque myelography showed that there was no obstruction to the flow of myodil upwards but confirmation was obtained of the increased capacity of the upper cervical spinal canal.

FIG. 4

It was considered that the disability resulted from compression of the upper cervical cord by protruding cerebellum. There was no clinical evidence of a cervical syrinx but a minor degree of cauda equina disturbance was presumed to be present.

Operation.—Cervical laminectomy under general anaesthesia was performed with removal of part of the occipital bone forming the back of the foramen magnum. The spinous process of the axis was abnormally large and the posterior arch of the atlas unusually thin, having a circular cross section of only $\frac{1}{8}$ in. diameter and constricting the dural tube which bulged above and below it. When the dura was opened the right cerebellar tonsil occupied the upper part of the spinal canal, was elongated and appeared pendunculated (Fig. 4). Beneath it the posterior spinal veins were congested and tortuous and the right inferior cerebellar artery was looped downwards. The exposure, particularly the removal of the thin posterior arch of the atlas, relieved the compression. The dura was left open to further the decompression.

Subsequent History.—The patient returned to his work as a carpenter three months after this operation. There is residual spasticity in the lower limbs but he leads a nearly normal life.

Case 2.—I. B., a housewife aged 49 years, was referred to Cardiff Royal Infirmary in October, 1956, with the complaint of increasing weakness of the legs. This had developed gradually over the previous 12 months and her gait was now slow and unsteady. She felt that the left lower limb was more affected than the right; in the past few months weakness had also made itself apparent in the left upper limb. She experienced short stabs of abdominal pain occasionally and at night she had been troubled with flexor spasms in the lower limbs. For two months her fingers and hands had become numb and clumsy and paraesthesia was intermittent. Her speech was becoming slurred.

FIG. 5.—Case 2: Scar of operation for removal of lumbosacral meningomyelocele in infancy.

FIG. 6.—Case 2: Atrophy of right side of the tongue.

Her previous history was interesting. She was born with a lumbosacral meningomyelocele which was removed at the age of 1 month. Her development was normal except that the left leg was thinner and $\frac{1}{2}$ in. shorter than the right. There was nocturnal enuresis persisting to adult life and periodic urinary incontinence by day. She played games in school but was rather clumsy. Occasionally she was unsteady on her feet. She had always found that her neck was "stiff"; she did not possess the normal amount of cervical mobility. She tended to turn her trunk when she wished to look sideways. At the age of 19 years she fell down a stairway in a store in which she was working and immediately lost the use of her legs. They were paralysed for five months and she was confined to her house for a year. No further particulars could be obtained about this episode and she had always understood that the paralysis resulted from injury to her spine. Her arms were not affected. Her legs were numb and there was defective urinary control.

She recovered, returned to her work, and led a moderately active life. Her gait was never wholly normal, she tired easily, could not dance, and a tendency to stumble persisted. She married but had no children. She had never suffered from blurring of vision, diplopia, or transient episodes of weakness or numbness of trunk or limbs. Her husband had noticed that at meals of late she frequently coughed and choked slightly. Swallowing was becoming difficult and there was nasal regurgitation at times.

On examination the scar of the lumbosacral operation was visible (Fig. 5) and there was some lack of development of the muscles of the left calf and foot. She was of slight build and walked unsteadily in a slow fashion. Her speech was slightly slurred and nasal, the optic discs and fundi were normal and the corneal reflexes were brisk. Palatal movements were weak and the right side of the tongue showed atrophy and fibrillation (Fig. 6). The jaw jerk was normal.

Movements of the neck were slightly limited in all directions but rotation and lateral flexion to the left were distinctly restricted. There was moderate diffuse

FIG. 7.—Case 2: Antero-posterior tomograph of the craniovertebral junction showing fusion of the odontoid to the left lateral mass of the atlas.

FIG. 8.—Case 2: Lateral tomograph of the craniovertebral junction showing fusion of spinous processes of atlas and axis and fusion of the odontoid to the clivus.

weakness of the left upper limb with slight wasting of the extensor muscles of the forearm and the dorsal interossei. The reflexes of the upper limbs were symmetrically exaggerated; the finger jerks were brisk. There was moderate weakness of both lower limbs, left more than right. Both knee jerks were exaggerated but the ankle jerks were absent. There were no plantar reflexes; the abdominal reflexes were absent. There was no defect of coordination in upper or lower limbs. All forms of superficial sensation were impaired in the left upper limb below the elbow and in both lower limbs below the knee; the impairment was most marked in the peripheral parts of these limbs. There was no area of dissociated sensory loss. Vibration sensation was absent in the left leg and impaired in the right. Appreciation of passive movements was defective in the fingers of the left hand and in the toes of both feet.

Radiological Examination.—There was a spina bifida involving the first and second sacral vertebrae. The foramen magnum and upper cervical spinal canal were of normal dimensions. There was a bony abnormality involving the atlas and axis, which was studied by tomography (Figs. 7 and 8). There was no basilar impression; the odontoid was fused to the left lateral mass of the atlas and also to the clivus where a false joint could be seen; the spinous processes of the atlas and axis were fused. The atlas was not " occipitalized ", there was no atlanto-axial dislocation, and the remaining cervical vertebrae were normal.

Lumbar puncture yielded a clear fluid with normal pressure and a protein content of 24 mg. per 100 ml. The Wassermann reaction was negative and manometry was normal.

Opaque Myelography.—The myodil column flowed freely upwards through the cervical region and no abnormality was detected.

Operation.—Upper cervical laminectomy under general anaesthesia revealed a fusion of the posterior arch of the atlas with the spinous process of the axis. There was no constriction of the dura, which, when opened, revealed a normal cord and cerebrospinal junction.

Subsequent History.—During the ensuing year her condition progressively deteriorated. The eyes remained normal; speech became more nasal and less distinct; there was loss of the left corneal reflex with hypoalgesia of the left trigeminal field; gross wasting and fibrillation of both sides of the tongue, dysphagia, palatal paresis, and marked wasting of the muscles about the shoulder girdle with fasciculation were noted. The muscles of both hands wasted and the arm reflexes disappeared. Spastic paraplegia was present with all forms of sensation impaired below th. 2-3. The pressure and composition of the cerebrospinal fluid remained normal. She died of suppurative bronchitis on October 17, 1957, two years after the onset of the illness.

Necropsy.—Dr. E. E. Payne made the necropsy examination. The spinal cord extended into the sacral canal: there was no lumbar enlargement of the cord but the dural sac in this region was dilated. The cord was tethered to the sacrum. Thin sagittal sections of the cervical spine and posterior fossa mounted on paper according to the Gough-Wentworth method (1949) showed fusion of the odontoid with the left lateral mass of the atlas. The tip of the odontoid was also fused to the clivus and the anterior arch of the atlas was displaced upwards and anteriorly. There was slight diffuse atrophy of the cerebral hemispheres with slight ventricular

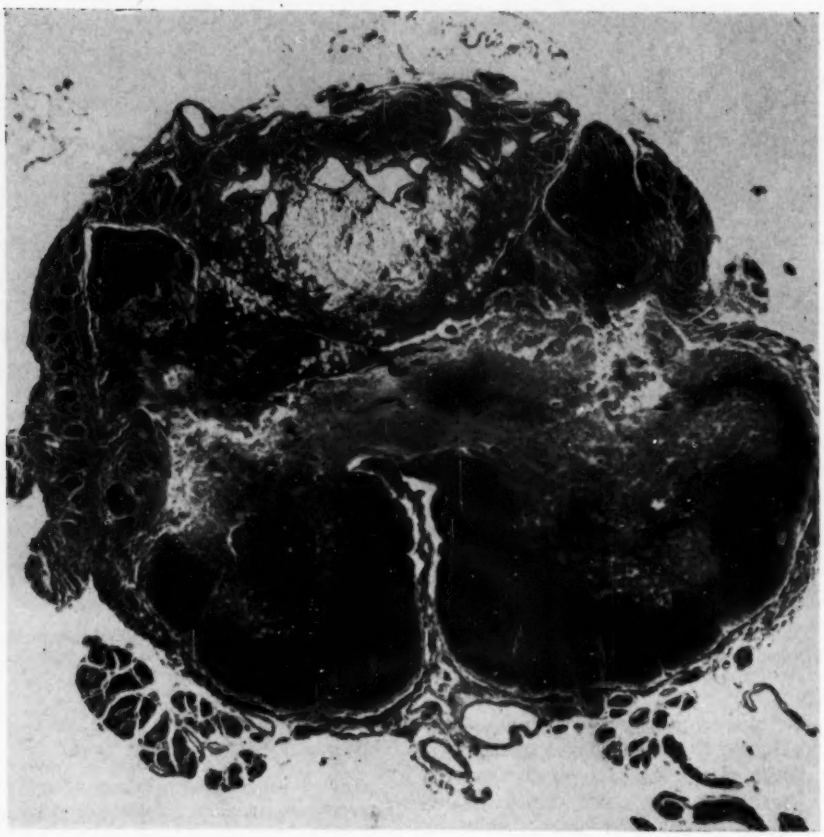

FIG. 9.—Case 2: Transverse section of the sacral spinal cord showing maldevelopment of posterior segments of the cord.

dilatation. There was no tumour or distortion of the brain-stem or cerebellum. A spindle-shaped area of degeneration approximately 1½ in. in length was seen in the anterior half of the medulla extending from its junction with the cervical cord below to the pons above.

Microscopical examination of the nervous system could not include the medulla as this had been sectioned *in situ* in preparing the thin sagittal sections of the cervical spine and base of the skull. The brain was microscopically normal. In the mid-brain many of the large ganglion cells contained pigment. In the thoracic cord there was chromatolysis and reduction in number of the anterior horn cells with sclerosis in the posterior and lateral columns. The architecture of the lumbosacral cord was grossly distorted: fat and fibrous tissue replaced the posterior segments (Fig. 9). Sections of muscle from the thenar groups, forearm extensors, and tongue showed fibre atrophy and sarcolemmal proliferation.

Commentary

We here have two adults with lumbosacral spina bifida and cranioverterbral anomalies presenting with a progressive neurological disturbance. In Case 1 there was spastic paraplegia, altered arm reflexes, nystagmus, and ataxia; radiological examination revealed an enlarged foramen magnum and upper cervical canal. Laminectomy disclosed compression of the cord from a herniated cerebellum projected through and itself compressed by an abnormal posterior arch of the atlas. In Case 2 there was progressive paraplegia and bulbar palsy together with sensory loss in the left trigeminal field, in the left upper limb and below th. 2-3. Wasting and fasciculation of the muscles of the upper limbs were observed. At operation there was no herniation of the cerebellum or deformity of the medulla and no syrinx or abnormal dural adhesion or membrane.

In the first case the diagnosis of cerebellar herniation was considered most probable in view of the enlargement of the foramen magnum. In the second there was no compressing lesion of the medulla or cervical cord. Disseminated sclerosis was excluded in virtue of the muscular wasting and fibrillation; pathological examination of the brain and thoracic cord disclosed no areas of characteristic demyelination. The paralysis of the legs at the age of 19 years

was considered to be due to injury to the congenital lumbosacral malformation, an occasional occurrence in patients with spina bifida cystica. (Concussion of the sac in Case 2 also tended to induce weakness and numbness of the lower limbs.) Motor neurone disease was excluded by reason of the sensory loss in the left upper limb and the left side of the face. The original sensory disturbance in the lower limbs may have been due to interference with the cauda equina but as the disease advanced all forms of sensation were impaired below upper thoracic levels. Although the classical zones of dissociated sensory loss of syringomyelia were not found it was thought that a degenerative lesion was present in the medulla and cervical cord which was in some way related to the congenital anomalies at the upper and lower ends of the spinal canal.

In retrospect it is unfortunate that the technique of post-mortem examination of the cervical spine and cord by the thin section method was adopted in this case. We thought it would help in disclosing the relationships between the craniovertebral anomaly and the lesion in the neuraxis. Macroscopic degeneration was revealed in the medulla but histological studies were then impossible for the reasons already given.

There are two aspects of these cases which are noteworthy, first, the problem of delayed neurological manifestations of spina bifida, and secondly, the question of the association with abnormalities at the foramen magnum.

It is well known that when they occur the neurological complications of lumbosacral spina bifida occulta may not make their appearance for some years—until late childhood or adolescence (Craig and Mulder, 1956). Laminectomy may then enable us to remove a pad of fat compressing the dura or sever adhesions or bands tethering or exerting traction upon the cauda equina or conus medullaris. In neither of our patients, however, was this the explanation: the neurological disability arose not at the caudal end of the spinal canal but at the craniovertebral junction and was therefore not due to the spina bifida.

Cerebellar herniation through the foramen magnum may be found in patients with or without craniovertebral anomalies and meningomyeloceles. In association with craniovertebral abnormalities in adult patients it has been observed by Chamberlain (1939), Gustafson and Oldberg (1940), List (1941), Craig, Walsh, and Camp (1942), Scoville and Sherman (1951) Garcin and Oeconomos (1953), Cogan and Barrows (1954), and by others. With a normal craniovertebral junction it has been reported by Aring (1938), McConnell and Parker (1938), Ogryzlo (1942), Bucy and Lichtenstein (1945), Gardner and Goodall (1950), and by others. Both types of case have been described by Spillane, Pallis, and Jones (1957). Although the term "Arnold-Chiari malformation" is usually applied to the deformity of the hind-brain in hydrocephalic infants with meningomyeloceles, Chiari (1895) also described cases in which there was no meningomyelocele and some of these patients reached adult life (six out of 14). He referred to these as type 1 and pointed out that the fourth ventricle was not displaced below the foramen magnum. The cerebellar "peg-shaped appendage" was often asymmetrical and sometimes unilateral. It is this type of malformation which was found in our first case. There was nothing to suggest that the cerebellar displacement was a result of "traction" from below or pressure from above. It is presumably an anomaly of development associated but not in any way dependent upon the grosser anomaly at the sacral end of the vertebral column.

Summary

Two cases are reported of the association of lumbosacral spina bifida cystica with craniovertebral anomalies.

Neurological disability arising from the lesion at the cranio-vertebral junction began at the age of 33 years in the first case and 48 years in the second case.

Operation disclosed a Chiari malformation (type 1) in the first patient. In the second case the appearances were normal but at necropsy a year later the only lesion consisted of a softening of the medulla and cervical cord.

There was no evidence in either case that anchorage, pressure, or traction on the neuraxis was primarily responsible for the lesion in the nervous system.

References

Aring, C. D. (1938). *J. Neurol. Psychiat.*, **1**, 100.
Bucy, P. C., and Lichtenstein, B. W. (1945). *J. Neurosurg.*, **2**, 245.
Chamberlain, W. E. (1939). *Yale J. biol. Med.*, **11**, 487.
Chiari, H. (1895). *Denskchr. Akad. Wiss. Wien (Math. natur. Klasse)*, **63**, 71.
Cogan, D. G., and Barrows, L. J. (1954). *Arch. Ophthal. (Chicago)*, **52**, 13.
Craig, W. McK., and Mulder, D. W. (1956). *Proc. Mayo Clin.*, **31**, 98.
——, Walsh, M. N., and Camp, J. D. (1942). *Surg. Gynec. Obstet.*, **74**, 751.
Garcin, R., and Oeconomos, D. (1953). *Les Aspects Neurologiques des Malformations Congenitales de la Charnière Cranio-Rachidienne. Masson Paris.*
Gardner, W. J., and Goodall, R. J. (1950). *J. Neurosurg.*, **7**, 199.
Gough, J., and Wentworth, J. E. (1949). Proc. 9th Int. Congr. industr. Med. (1948), p. 661.
Gustafson, W. A., and Oldberg, E. (1940). *Arch. Neurol. Psychiat. (Chicago)*, **44**, 1184.
List, C. F. (1941). *Ibid.*, **45**, 577.
McConnell, A. A., and Parker, H. L. (1938). *Brain*, **61**, 415.
Ogryzlo, M. A. (1942). *Arch. Neurol. Psychiat. (Chicago)*, **48**, 30.
Scoville, W. B., and Sherman, I. J. (1951). *Ann. Surg.*, **133**, 496.
Spillane, J. D., Pallis, C., and Jones, A. M. (1957). *Brain*, **80**, 11.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 50.

THE RELIEF OF MYOTONIA BY THE USE OF A POTASSIUM-BINDING RESIN

BY

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The phenomenon of myotonia comprises a lingering relaxation of muscle after contraction, and a slow tonic response to stimuli of an electrical or mechanical nature. The condition may be ameliorated or even extinguished by repeated effort. Although well known and the commonest form of hereditary muscular disorder seen in young adults, it is, nevertheless, a rare condition.

Three distinct forms of the disturbance are recognized: (*a*) Myotonia congenita, where the disability exists in a simple form; (*b*) myotonia atrophica, in which disease the defect is associated with muscle wasting of typical distribution; and (*c*) paramyotonia congenita, a disorder in which myotonia and weakness are especially prominent on cooling and may be associated with muscle atrophy. It is doubtful whether the three conditions are in fact entities and there is much overlapping between them. The literature of these conditions has frequently been reviewed, most recently by de Jong (1956) and can probably best be summarized by saying that so far no unanimity has been arrived at either in describing the physiological or pathological factors underlying the condition or in arriving at a uniformly satisfactory method of treatment for the disability.

Liversedge and Newman (1956) reported on the satisfactory effect of cortisone in myotonia and concluded that it was probably due to a modification of the susceptibility of the muscle cell membrane to potassium ions. They were in doubt as to whether the actual elimination of potassium from the body was a factor. It was felt that this point could be further settled by a procedure specifically directed towards removing potassium, the more so since long-continued administration of cortisone is frequently accompanied by undesirable side-effects which may be serious (Allanby, 1957). It was decided to investigate the effect of a potassium-binding ion-exchange resin for this purpose. This method of treatment had previously been used by Grüttner and Mertens (1953) in a case of myotonia congenita with satisfactory results but has not been reported before in Great Britain and there is no record of the results of treatment of a case of myotonia atrophica. Incidental investigation was made into the biochemical changes caused by exhibition of quinine and procaine amide as control substances.

Methods

Relaxation time was recorded by Chief Technician W. Glayzer using the method of Liversedge and Newman (1956) with surface electrodes and an eight-channel Ediswan electroencephalograph.

Muscle power was recorded under the direction of Squadron Leader Lough using a dynamometer.

Electromyography was carried out by Wing Commander P. R. Travers and Squadron Leader C. B. Wynn Parry, M.B.E., of the Royal Air Force department of Physical Medicine, using concentric needle electrodes.

Total and differential blood counts, Wassermann and Kahn reactions, chest radiographs, E.C.G., E.E.G., and slit lamp examination of the eyes were carried out on admission.

Serum sodium, potassium, chloride, and bicarbonate levels were estimated twice weekly and calcium, phosphate, magnesium, cholesterol urea, creatine, and creatinine once or twice weekly. Serum proteins, liver function tests, blood sugar and total lipid and phosphate fractions were also estimated on admission and a glucose tolerance test carried out. Urinary sodium and potassium were measured daily throughout the course of treatment and urinary creatine and creatinine, 17-oxysteroids, and total ammonia and titratable acidity estimated once weekly. The results of these tests are only included when thought significant.

Case Reports

Case 1.—An 18-year-old airman was referred to hospital after weakness in the muscles of the right forearm and hand had been discovered at a routine medical examination.

He stated that for several years he had experienced difficulty in keeping his mouth closed, especially when tired, and in addition his tongue appeared to " tighten up " after he had been speaking for some time. Further questioning revealed that a younger brother aged 12 had begun to experience similar symptoms. No other

member of the family was affected as far as could be ascertained, and there was no familial history of cataract.

On examination he was a well-nourished boy with incipient frontal baldness, facial atrophy, and weakness of the peri-oral muscles. The sternomastoids and shoulder muscles were grossly atrophic, giving him a swan-necked appearance. The muscles of both forearms and hands, particularly the right, were wasted and he had extreme difficulty in writing more than a few sentences. Myotonia was present in the muscles of both hands and he required several seconds to release his grip after a hand shake. Percussion myotonia of the tongue and shoulder muscles was elicited.

A chest radiograph, E.C.G., E.E.G., blood count, Wassermann and Kahn and slit-lamp examinations were all normal.

An electromyogram on February 18, 1957, on the extensors of the right forearm showed the classical picture of dystrophia myotonica. Exceptionally high frequency discharges on volition of small duration but normal amplitude were obtained. On tapping the muscle a prolonged outburst of high frequency discharges with a pronounced after-discharge was obtained. Similar but less obvious signs were seen in the right biceps.

The serum potassium level was 6 mEq./l., serum sodium 152 mEq./l., plasma chloride 107 mEq./l., plasma bicarbonate 31·2 mEq./l., blood urea 25 mg. per 100 ml.

The serum calcium level was 5·9 mEq./l., phosphate 4·1 mg. per 100 ml., magnesium 2·8 mg. per 100 ml., serum cholesterol 149 mg. per 100 ml., serum creatinine 1·16 mg. per 100 ml., and creatine 0·30 mg. per 100 ml.

The urinary sodium was 320 mEq. in 24 hours and potassium 115 mEq. in 24 hours. The output of 17-oxysteroids was 6 mg. in 24 hours and creatinine 1·5 g. in 24 hours. No creatine was present.

The fasting blood sugar was 75 mg. per 100 ml. and a glucose tolerance test gave a very flat curve. This was not due to glucose being delayed in the stomach as a barium swallow showed a normal rate of emptying.

Serum protein and liver function tests were normal and estimations of phosphate and lipid fractions gave results which were within normal limits.

The relevant findings on the case are charted in Fig. 1.

The patient was observed for four weeks and on April 4, 1957, potassium exchange therapy was started. The initial dosage of " resonium A " was 45 g. per day taken in three divided doses of 15 g. with meals. This was continued until April 18, 1957, when, as the serum potassium had dropped to 3·8 mEq./l. the resin was stopped for one day and then re-started in a dosage of 15 g./day. This dosage was continued until April 29,

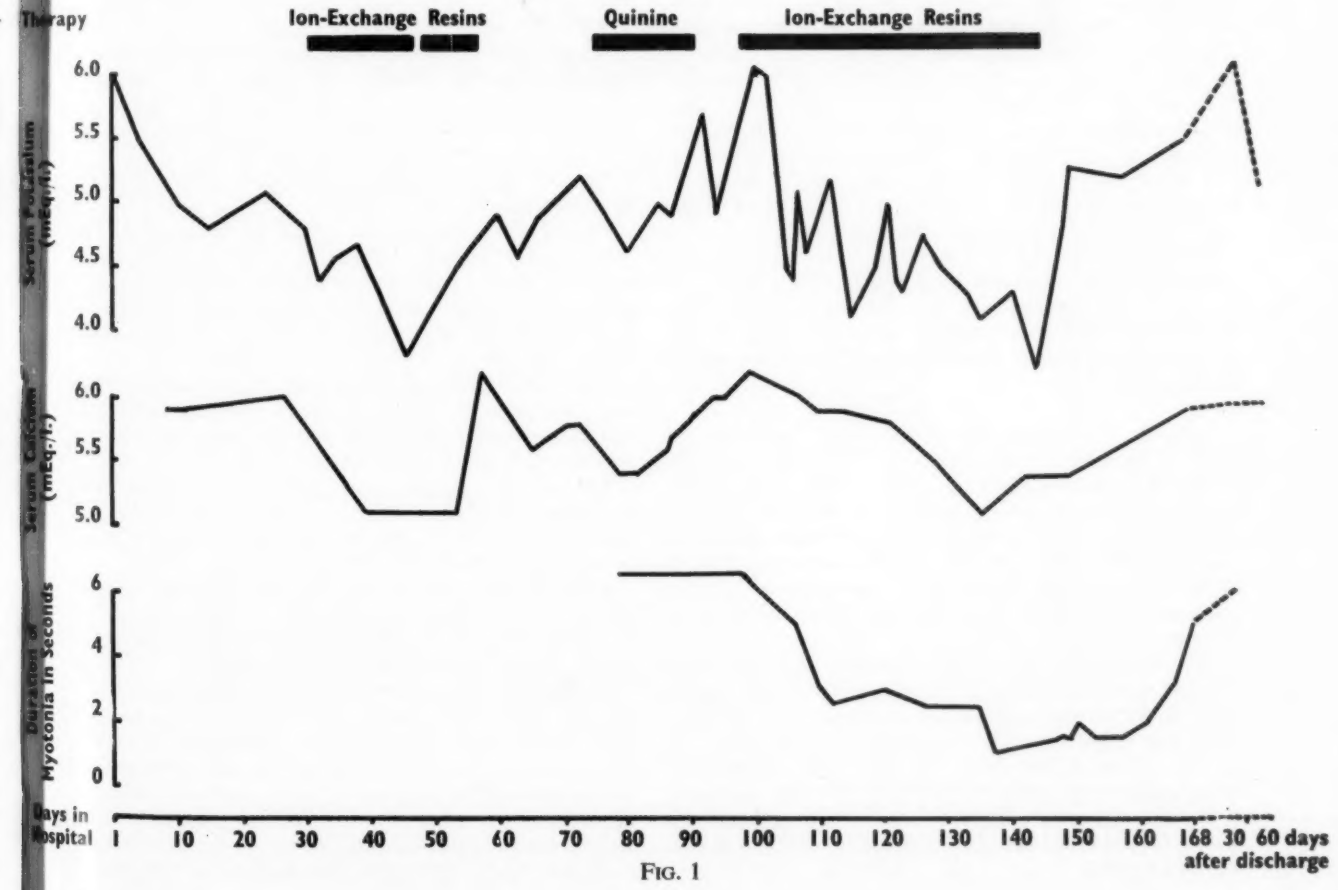

FIG. 1

1957, when the treatment was stopped as our attention had been drawn to the paper of Liversedge and Newman and we wished to use their method of measurement of myotonic time.

The strength of the hand grip was originally 12 lb., but under treatment it increased until it reached a maximum of 44 lb. on April 22, 1957. Thereafter it fell progressively with cessation of treatment to its previous level of 12 lb.

On May 18, 1957, treatment was started with quinine dihydrochloride as a control, given as one 5-grain tablet four times a day. At this dosage level the patient complained of tinnitus so the dosage was adjusted until the amount of quinine given was just below that which would cause tinnitus. This was found to be 15 grains per day and the patient was maintained on this until June 2, 1957. No subjective or objective relief was gained.

On June 10, 1957, a second course of potassium-binding resin was begun in a dosage of 30 g. three times a day. The duration of myotonia began to drop from values in the region of 6 to 7 sec. and the power of the right hand began to increase within a few days of the start of the treatment. On June 27, 1957, a second electromyogram was carried out with the following report:—

" On volition there were predominantly normal action potentials with only a very few typical high frequency discharges. Percussion of muscle produced only a transient increase in the rate of fibrillation and no true myotonia. The myographic picture appears to have changed to a marked extent as compared to that obtained on May 27, 1957."

Treatment was continued and by July 2, 1957, the patient was able to write sufficiently freely to sit a university entrance examination. The duration of myotonia had decreased to about two seconds and the power of his grip had risen again to a value in the region of 40 lb. On July 26, 1957, treatment was stopped.

During the periods of resin therapy there was a marked decrease in excretion of urinary potassium. In this time the patient did not become acidotic, the bicarbonate level never falling below 25 mEq./l. and there was no change in serum or urinary levels of creatine of creatinine.

Case 2.—A 21-year-old airman was admitted to hospital complaining of stiffness of his hands and legs dating from early childhood. This stiffness was most noticeable when he attempted to move suddenly after a period of rest. Three months before admission he had a fall while playing cricket and on the following day he found he was unable to release his hand grip. As far as we could ascertain no other members of the family were affected.

On examination he was a well-built, muscular boy. He had myotonia in both hands and percussion myotonia could be demonstrated in the muscles of the forearms and shoulders. There was no measurable loss of power. The patient was not very cooperative and investigation and treatment were reduced to a minimum.

A chest radiograph, E.C.G., E.E.G., Wassermann and Kahn reactions, blood counts, and slit-lamp examination were all normal.

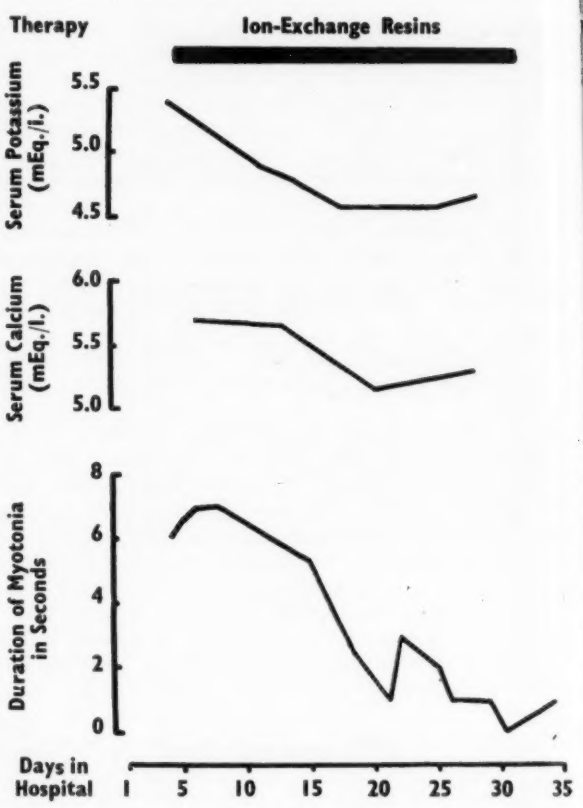

FIG. 2

An electromyogram gave a classical picture of myotonia congenita.

The serum potassium level was 5·4 mEq./l., sodium 141 mEq./l., chloride 104 mEq./l., and plasma bicarbonate 23 mEq./l., serum cholesterol 210 mg. per 100 ml., and urea 33 mg. per 100 ml., serum calcium 5·7 mEq./l., inorganic phosphate 4·5 mg. per 100 ml., and magnesium 2·3 mg. per 100 ml.

The blood sugar was 90 mg. per 100 ml. and a glucose tolerance test gave a normal curve. Liver function tests and estimations of phosphate and the lipid fraction gave results which were within normal limits.

The urinary sodium was 191 mEq./24 hours and potassium 66 mEq./24 hours. The output of 17-oxysteroids was 2·1 mg./24 hours, creatinine 1·9 g./24 hours, and creatine 0·2 g./24 hours.

Treatment was started on June 24, 1957, with potassium-binding resin (" resonium A ") in a dosage of 30 g. three times a day. The myotonia improved markedly within a short time, as shown in Fig. 2.

Subjectively the patient noted the stiffness in his legs had practically gone and he was able to release his grip much more easily than before. Percussion myotonia could no longer be elicited after three weeks of treatment, which was stopped on July 22, 1957. A second electromyograph was refused. The serum potassium and calcium levels dropped slightly but not to the same degree as in Case 1. No other biochemical changes were noted.

Case 3.—An airman of 19 was admitted complaining of inability to release the grip of both his hands and of increasing stiffness in his jaw since the age of 16. His father was found to be suffering from the same disease, and in his case the symptoms appeared when he was aged 35.

On examination he was found to be a well-built youth. He had marked myotonia both in the jaw muscles and in the hands. Percussion myotonia could be demonstrated in the jaw, tongue, and both arms, There was no loss of power.

A chest radiograph, E.C.G., E.E.G., slit-lamp examination, Wassermann and Kahn reactions, and blood counts were all normal.

An electromyogram was carried out on July 4, 1957, with the following reports:—

" A needle electrode was inserted into the flexor carpi ulnaris. Positive insertion potentials. At rest irregular fibrillation potentials with some sporadic isolated muscle potential of up to 300 mv. was elicited and on volition profuse activity with high frequency potentials of up to 1,800 mv. Considerable after-activity continued for about seven to eight seconds after voluntary relaxation had begun. A myotonic response was obtained on percussion of a muscle belly. The changes were characteristic of myotonia."

The serum potassium level was 4·9 mEq./l., sodium 136 mEq./l., chloride 111 mEq./l., plasma bicarbonate 28·8 mEq./l., blood urea 34 mg. per 100 ml., serum calcium 5·7 mEq./l., phosphate 4·5 mg. per 100 ml., magnesium 2·9 mg. per 100 ml., serum cholesterol 135 mg. per 100 ml., serum creatinine 1·1 mg. per 100 ml., and creatine 0·23 mg. per 100 ml. Liver function tests, serum proteins, and estimations of phosphate and lipid fractions were all within normal limits.

The urinary sodium was 238 mEq./24 hours, potassium 107 mEq./24 hours, 17-oxysteroids 8·3 mg./24 hours, creatinine 2·7 g./24 hours, and creatine 0·16 g./24 hours.

Treatment was begun on July 9, 1957, with procaine amide hydrochloride as a control in a dosage of 0·5 g. four times a day. On July 16, 1957, the dosage was increased to 3 g. daily but at no time were any beneficial results obtained and the therapy was stopped on July 19, 1957. Treatment with ion exchange resin was begun on July 21, 1957, in a dosage of 30 g. three times a day with steady response. This dosage was increased to 45 g. three times a day one week later with further improvement. Because of side-effects it was impossible to maintain the increased dosage of resin and it was decided to attempt to potentiate the effect of the lower dose of the resins by increasing potassium excretion. Diamox

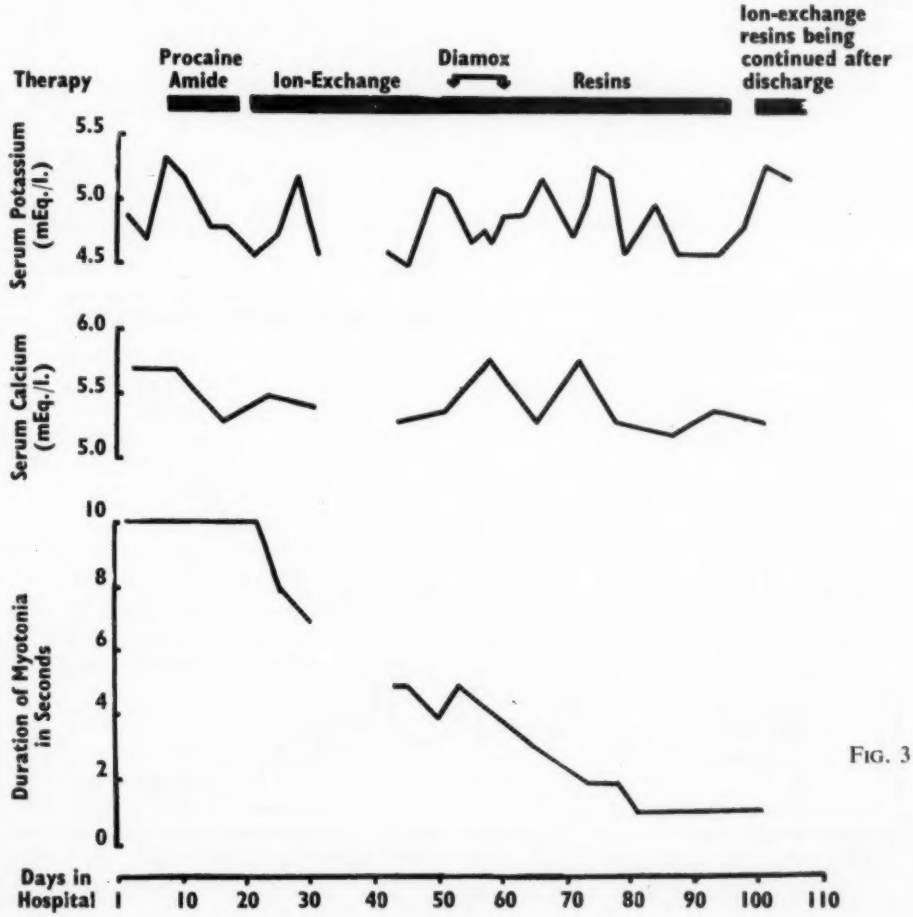

FIG. 3

(acetazolamide) was given for one week for this purpose but proved ineffective. However, progress continued on the lower dosage. The patient found he could release his grip much more easily than before and the percussion myotonia could no longer be elicited. A second electromyogram was carried out on September 11, 1957, showing a very marked change in the myographic picture. (1) There was practically no insertion potential. (2) There was no electrical activity at rest. (3) There were very few high-voltage potentials on volition and the interference pattern was now almost normal. (4) Electrical activity died away within two or three seconds of voluntary relaxation. These changes showed a considerable return towards normality in the myographic picture.

The patient has been discharged on the resin and his improvement has been maintained. His father, who suffers from the same disease and has been treated with procaine amide, regards the improvement as so satisfactory that he wants to start taking potassium-binding resins himself.

Discussion of Biochemical Results

All three patients obtained objective and symptomatic relief from myotonia when treated with the potassium-binding resins.

The only biochemical changes of note obtained during therapy were in the serum potassium and calcium levels.

In Cases 1 and 2 (Figs. 1 and 2) the fall paralleled closely the clinical improvement of the patients as judged by a decrease in the degree of myotonia. On cessation of treatment on two occasions in Case 1, the serum potassium and calcium rose to their pre-treatment level as the myotonia returned.

In Case 3 there was no significant change in serum potassium or calcium level and yet the myotonia improved rapidly (Fig. 3). The explanation of this may be simply due to the fact that this patient was allowed home frequently and that the rise of serum potassium closely paralleled these visits, possibly due to the fact that the patient did not take the resins while at home. On the other hand, it may be that the action of these resins is not simply to lower extracellular potassium but also the intracellular potassium. This would be followed by a movement of sodium into the cell and the relief of the myotonia might be due to alterations in the extracellular/intracellular ratio of sodium. Against this is the fact that neither in this case nor in the other two cases were there any changes in the serum sodium. To elucidate this point further, assays of intracellular potassium and sodium should be carried out during treatment with these resins.

The fall in serum calcium in Cases 1 and 2 was comparatively slight and it is improbable that by themselves these changes could cause any significant changes in the muscle excitability. There was also no significant alteration in the serum potassium/calcium ratio which could account for the clinical improvement in these cases.

None of the patients became acidotic, the plasma bicarbonate staying within normal limits in all the cases.

The urinary excretion of potassium was decreased in all the patients during resin therapy as illustrated in Case 1 (Fig. 4). Serum and urinary creatine and

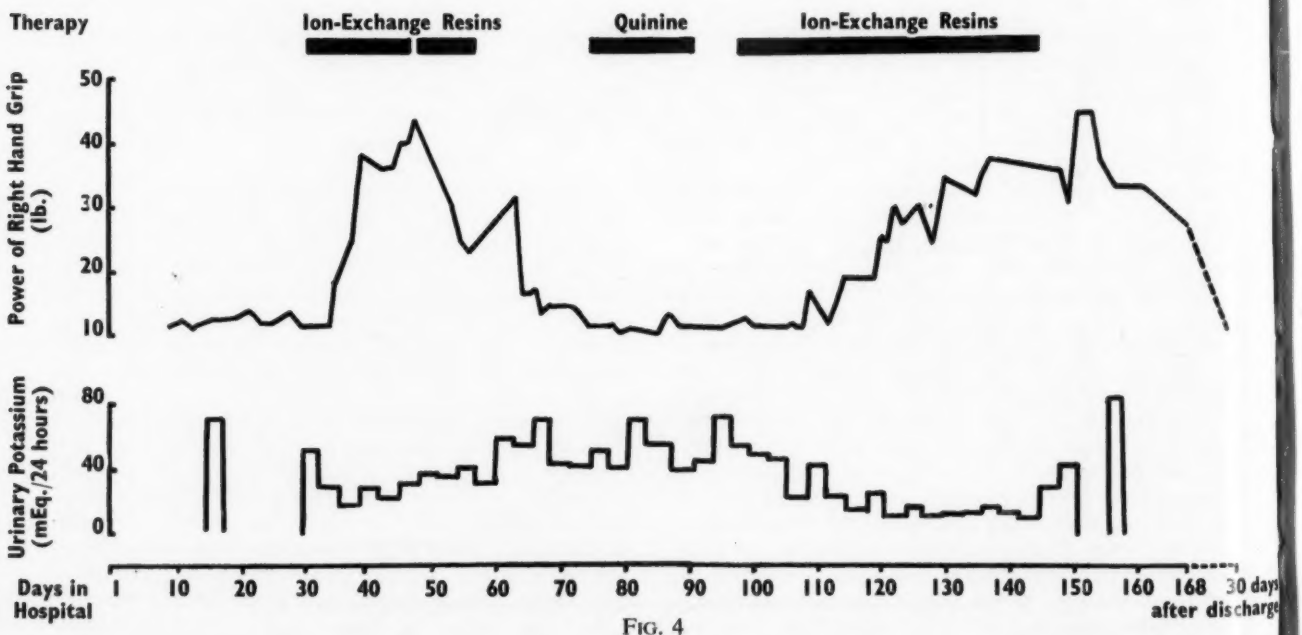

FIG. 4

creatinine levels showed no alterations during treatment.

No biochemical changes of significance were noted during treatment with quinine in Case 1 or procaine amide in Case 3.

Discussion

The relationship between muscle function and potassium has recently been reviewed by Grob, Liljestrand, and Johns (1957), and they point out that the resting potential difference in muscle cell membrane is principally related to the difference of potassium concentration between the inside and outside of the cells. This resting potential difference largely determines the excitability of the muscle since the lower the resting potential the more easily it is depolarized and *vice versa*.

In myotonic muscle the intracellular potassium may be reduced by as much as one half (Cumings, 1939). In the presence of a normal extracellular (serum) potassium level it is apparent that the resting potential of such muscle will be materially lowered and the muscle show increased excitability. Since the ratio in man between intra- and extracellular potassium is roughly 30 to 1 and the dependence of resting potential on the potassium differential is a logarithmic one (Ling and Gerard, 1949), a small lowering of extracellular potassium can compensate for a marked change in the intracellular content. It has, moreover, been shown by Flear, Cooke, and Quinton (1957) that there is no interdependence between the exchangeable body potassium and the serum potassium, so that quite wide variations in intra- and extra-cellular movement can take place without any linked effect.

In our experiment which resulted in a decrease of extracellular potassium it seems reasonable, therefore, to assume little change in the decreased intracellular potassium and to explain the decrease of myotonic irritability as being directly due to a reduction of muscle excitability. That this is a fundamental factor is supported by the fact (Norris and Chatfield, 1955) that action potentials which entirely parallel those found in myotonia may be seen in the pure dystrophies and in denervated muscle, in which the intracellular potassium may be similarly reduced. At our request Wing Commander Travers carried out the following experiment.

The arm and hand of a normal control were immersed in cold water at 40° F. until cramp was produced by voluntary effort.

> " Normal interference pattern with inlays of short duration potentials were seen. These resembled those in untreated myotonia. On allowing the limb to warm up the myograph tracing returned to normal and no cramp was experienced."

The effect of cold is decremental of intracellular potassium and is the trigger factor in the variety of the condition known as paramyotonia. It is our contention that the basic factor in myotonia is an alteration in muscle excitability due to shift in the potassium ratio, and that similar electrical findings can be demonstrated in muscle whenever minimal excitability occurs either for physiological or pathological reasons.

There are, however, certain distinctive features in myotonia which cannot be accounted for on this simple basis. First, in our experiment the power of muscle action in the case of dystrophia myotonica showed an increase with treatment and resulting decreased muscle excitability. The work of Grob, Johns, and Harvey (1957) demonstrated that in normal muscle increased muscle excitability resulted in increased power. Secondly, the same authors found that exercise resulted in a decrease of intracellular potassium. It would be expected, therefore, that repeated contractions of myotonic muscle would cause a similar lowering of intracellular potassium with heightened excitability and exaggeration of the myotonic response. The contrary is the case and the myotonic state works off with repeated movement. Thirdly, the specific action of myotonic muscle which is seen clinically as a symptom and electrically as " dive bomber " potentials has no parallel in the other conditions of lowered intracellular potassium. It is apparent that these distinctive features occur only under conditions of stimulation of the muscle either by nervous impulse or mechanical stress.

The action of both these stimuli is mediated by the release of acetylcholine and we suggest that the specific factor in myotonia is a defect in acetylcholine action. The action of acetylcholine in producing muscle contractions depends on two factors. First the excitability of the muscle, and secondly the available concentration of acetylcholine. In the presence of the state of easy depolarization produced by a low intracellular/extracellular potassium ratio, the initial clinical myotonic response to release of acetylcholine by stimulus is easy to understand. The particular phenomenon of working off could be explained if a mechanism existed whereby acetylcholine in excess was initially made available by stimulus and the source rapidly exhausted. This could presumably occur if myotonic muscle had an intrinsic defect of acetylcholine binding power comparable to that demonstrated in epileptic cerebral cortex (Tower, 1952).

It remains to comment on our finding of increased muscle power in the case of myotonia atrophica concurrent with decreased muscle excitability. Grob *et al.* (1955) showed that in the presence of

free acetylcholine muscle fails relatively in its ability to contract within half a minute, possibly by the setting up of a non-polarizable block and that this may last for up to half an hour. If we are correct in our assumption of an excess of free acetylcholine in myotonic tissue the loss of power can be accounted for by such a mechanism.

Summary

Two cases of myotonia congenita and one case of myotonia atrophica were treated with potassium-binding resin and showed objective and subjective relief.

Myotonia was greatly diminished in all cases and the abnormal electromyograms restored to normal form. In the case of myotonia atrophica the muscle power was greatly increased.

An explanation of the results is offered on the basis of the effect of potassium on the resting cell potential.

A hypothesis is advanced as to the pathology of the condition.

Our thanks are due to the Director General of Medical Services, Royal Air Force, for permission to publish this paper, to Corporal Technician McGhee for carrying out many of the biochemical investigations, to Dr. A. T. Richardson of the Royal Free Hospital for his helpful criticisms, and to the medical and nursing staff of Princess Mary's Royal Air Force Hospital, Halton.

References

•Allanby, K. D. (1957). *Lancet*, **1**, 1104.
•Cumings, J. N. (1939). *Brain*, **62**, 153.
•Flear, C. T. G., Cooke, W. T., and Quinton. A. (1957). *Lancet*, **1**, 458.
•Grob, D., Johns, R. J., and Harvey, A. M. (1955). *Amer. J. Med.*, **19**, 684.
•——, Liljestrand, Å., and Johns, R. J. (1957). *Ibid.*, **23**, 340.
•Grüttner, R., and Mertens, H. G. (1953). *Klin. Wschr.*, **31**, 868.
•Jong, J. G. Y. de (1956). *Dystrophia Myotonica, Paramyotonia and Myotonia Congenita*. Van Gorcum, Assen.
•Ling, G., and Gerard, R. W. (1949). *J. cell comp. Physiol.*, **34**, 383.
•Liversedge, L. A., and Newman, M. J. D. (1956). *Brain*, **79**, 395.
•Norris, F. H., and Chatfield, P. O. (1955). *Electroenceph., clin. Neurophysiol.*, **7**, 391.
Tower, D. B. (1952). *Epilepsia* (*Boston*), 3rd Series, **1**, 88.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 57.

THE ESTIMATION OF MOTILITY DURING REST OR SLEEP

BY

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It has been suggested that motility during sleep bears a reciprocal relation to depth of sleep (Pai, 1950). Kleitman (1932) and Maliniak (1934) describe mechanical or pneumatic systems for determining sleep motility, and Kleitman refers also to a photo-electric device which interpolates movements from the frequency of interruption by the sleeper of a source of light directed on to the bed (Kleitman, 1944).

The effect of drugs on movement during sleep might therefore be utilized as one criterion of the value of hypnotics. Yet methods for measuring sleep motility have been disappointing, the apparatus being cumbersome, or by virtue of its activity likely to keep the subject awake, or, when none of these demerits were applicable, the results obtained were difficult to quantitate. It is not surprising that Lasagna, in a recent appraisal of the efficacy of hypnotic agents, relied upon a combination of direct observation of the subject at intervals during the night together with the patient's estimate of sleep (Lasagna, 1954).

The apparatus here to be described operates on simple electronic principles and provides a reliable objective estimate of the amount of movement while the subject is recumbent or asleep.

Apparatus

The instrument is based on that designed originally by Mr. W. D. Furneaux. This consisted of four plungers arranged to lie under the transverse and longitudinal dimensions of the bed, the caps at the upper ends of the plungers being adjusted to make contact with the under surface of the mattress wire only if the subject was recumbent. The lower ends of the plungers abutted on to microswitches operating on the make-and-break principle, all four being connected in parallel. A downward displacement of any of the plungers completed the circuit, the resultant potential operating a counter remote from the ward. Furneaux found a reasonable correlation between motility scores obtained on this bed and a nurse's rating of the patient's depth of sleep (Furneaux, personal communication).

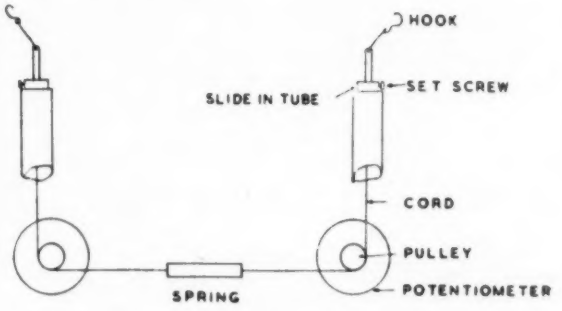

FIG. 1.—Semi-diagrammatic version of the apparatus mounted under the patient's bed.

We substantially modified this apparatus, some of its disadvantages being eliminated.

The plunger system was replaced by a cord drive (Fig. 1) connected above through an adjustable slide to a hook attached to the mattress wire. Below, the cord makes two revolutions (not shown in Fig. 1) around a brass pulley, as a single revolution was inclined to slip. Tension in the cord was maintained by a central spring. The slide (and cord length) is adjusted to the displacement of the mattress wire with the subject lying motionless in bed so that the relay just fails to operate. The microswitches were replaced by four standard linear carbon potentiometers (only two shown in Fig. 1), each attached to one of the brass pulleys. Movements at the pulley will therefore produce voltage differences at the potentiometer, the greater the movement the larger the potential difference. This voltage change was fed into the circuit shown in Fig. 2 and amplified at the 6J6 valve to provide enough current to work the Veeder-Root counter from which scores were read hourly from 10 p.m. to 6 a.m. (total motility scores). Hourly scores were obtained, as it was hoped in a drug trial, to ascertain the earliest moment at which drug effects were detectable. A pen recorder could be incorporated in the circuit if required.

Validation of the Bed

It was essential to show that scores obtained with the bed were consistent, that is to say, that no variations that could be ascribed to outside influences (drugs) were being introduced by imperfect functioning of the apparatus. Secondly, while it was surmised that the bed measured movement, corroboration had to be obtained by correlating the motility scores with ratings of restlessness by

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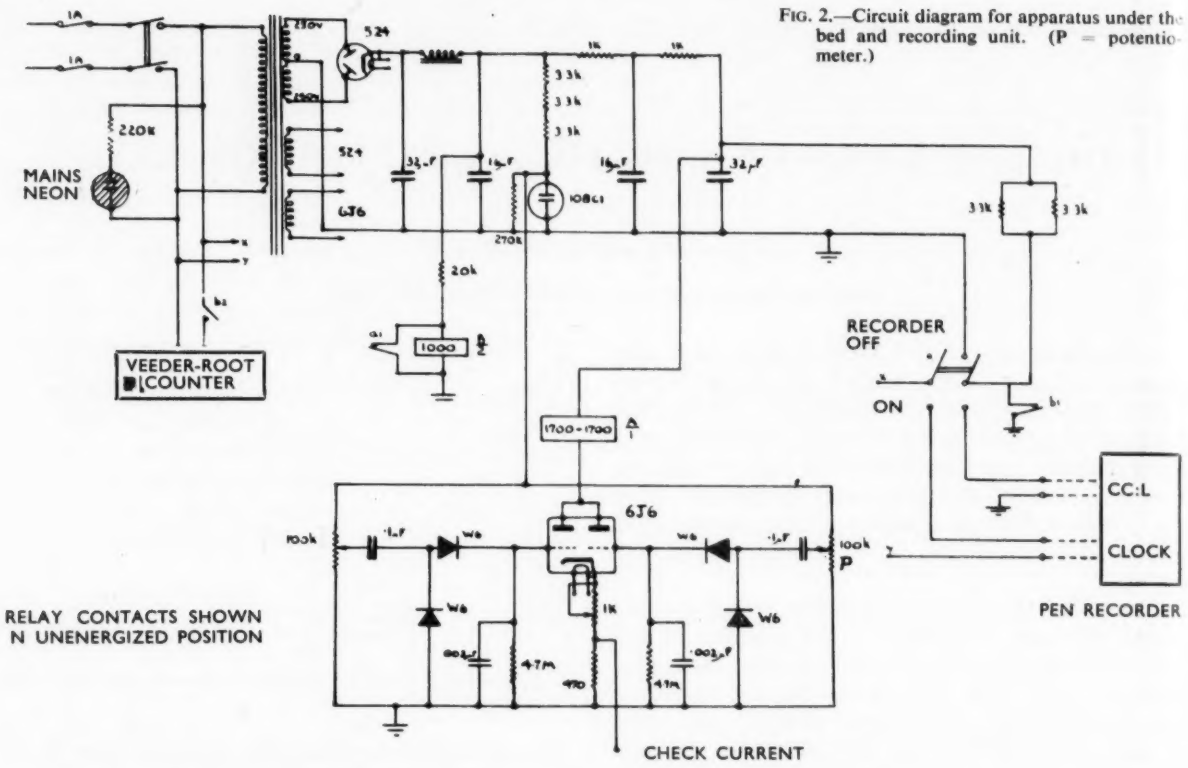


FIG. 2.—Circuit diagram for apparatus under the bed and recording unit. (P = potentiometer.)

observers (nurses and patients), nurses' ratings of sleep or restlessness being traditionally more reliable than those of the patient.

Reliability of the Apparatus

This was tested by two investigations. The first consisted of analysing the total motility scores between 10 p.m. and 6 a.m. for seven patients who had been sleeping on the bed for at least two nights before beginning a five-day trial (Table I). This stricture was imperative, as unrepresentative high scores were always returned for the first night on the bed of the patient being tested. The seven patients were men aged 31 to 60 years. Four of the seven suffered from depressive illnesses, two were chronic alcoholics withdrawn from alcohol for at least four weeks, and the last was a patient with "psychogenic vomiting". Four of the seven continued their night hypnotic (200 mg. amylobarbitone sodium) throughout the test phase, two received pentobarbitone sodium, 200 mg., and one slept without medication. The results were subjected to analysis of variance. Only that part of the variance due to the difference between patients was significant ($F = 3{\cdot}92$, $P < 0{\cdot}01$). The difference between mean motility scores for the five consecutive nights can therefore be assigned to the difference between subjects and not to a significant variation in function of the bed during the test period.

The results for the second part of the investigation (Table I) derived from 11 patients undergoing a drug trial during which they received placebo (alternating with other drugs) on three nights during each of two consecutive series both extending over nine nights. Fuller

TABLE I

MEAN, RANGE, AND STANDARD ERROR OF THE MEAN OF MOTILITY SCORES DERIVED FROM SEVEN PATIENTS RECEIVING EITHER MEDICATION OR NO MEDICATION AND 11 SUBJECTS RECEIVING PLACEBO

Number of Patients	Motility Scores	Indices (units)	Nights					
			1	2	3	4	5	6
7	10 p.m. to 6 a.m.	Mean	51·4	45·3	38·0	37·7	56·3	—
		Range	9-100	9-117	20-65	10-64	12-116	—
		S.E. of Mean	11·5	12·5	5·9	6·4	13·4	—
11	10 p.m. to 2 a.m.	Mean	42·4	41·9	35·0	33·0	31·3	34·7
		Range	5-134	5-117	7-92	1-82	8-99	6-110
		S.E. of Mean	11·1	11·1	8·2	7·9	7·8	9·8
	10 p.m. to 6 a.m.	Mean	77·1	80·1	67·5	65·6	62·5	67·2
		Range	15-236	12-223	9-152	11-140	8-176	16-155
		S.E. of Mean	19·6	20·1	13·8	12·4	14·0	12·2

FIG. 3.—Scatter diagram of total motility scores (10 p.m. to 6 a.m.) and nurses' rating for seven patients on five consecutive nights.

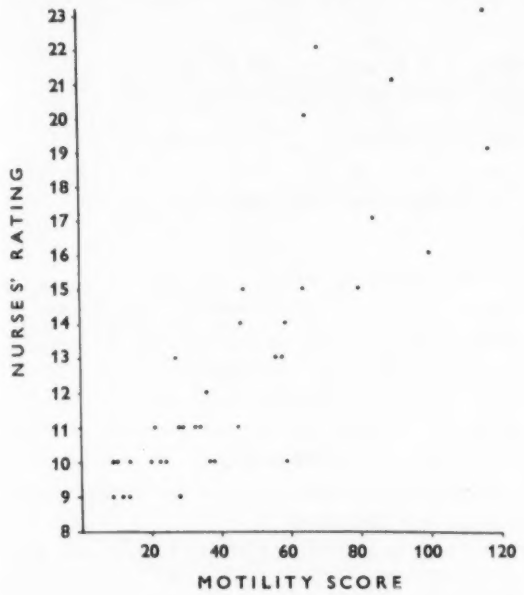
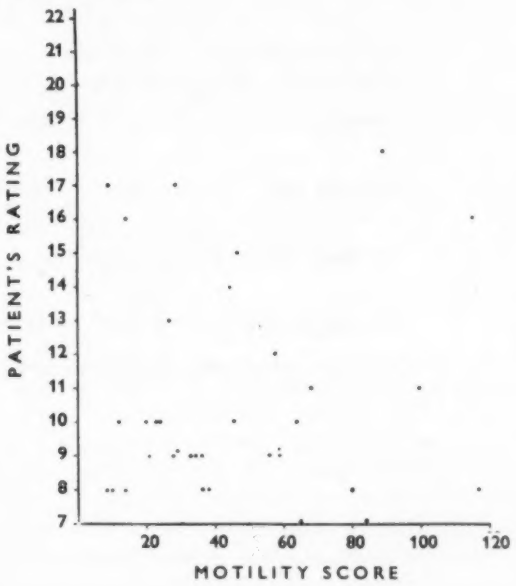


FIG. 4.—Sleep questionnaire completed by patients each morning. Figures in parentheses represent arbitrary rating for each item of the five questions.



details are included in a further paper (Hinton and Marley, 1959). Total motility scores between 10 p.m. and 2 a.m. and 10 p.m. and 6 a.m. were examined by analysis of variance. The only significant contribution to the total variance for the scores between 10 p.m. and 2 a.m. came from the differences between patients ($F = 8{\cdot}84$, $P < 0{\cdot}01$) as was also the case for the motility scores between 10 p.m. and 6 a.m. ($F = 13{\cdot}24$, $P < 0{\cdot}001$).

Thus the actual functioning of the bed as determined either from motility scores for part of (10 p.m. to 2 a.m.) or the whole of the night (10 p.m. to 6 a.m.) can be excluded as a significant source of difference in motility scores.

Nurses' Rating and Motility Scores

The motility scores were recorded hourly by one nurse for each of the original seven patients between 10 p.m. and 6 a.m. At the same time another nurse was required to give an independent estimate of the patient's restlessness (sleep) during the prescribed hour. An arbitrary rating was adhered to, that of 1 for normal sleep, 2 for mild restlessness, 3 for moderate restlessness, and 4 if the patient should be excessively restless (8-32 = minimal-maximal night rating). Fig. 3 is a scatter diagram of the nurses' rating (ordinate) plotted against the respective nightly total motility scores of each patient (abscissa) during the five-day period. The correlation between the two was significant ($r = +0{\cdot}81$, $P < 0{\cdot}01$). Thus movement as measured by the apparatus correlates highly with the nurses' ratings of movement.

Patients' Rating and Motility Scores

A "five-question" questionnaire (Fig. 4) was presented each morning to the seven subjects during the five-day trial period. (This was evolved by Dr. D. L. Davies and had been used by him in a previous drug investigation.) The questionnaire was arbitrarily scored (figures within brackets) so that an evaluation might be derived from the patient's own estimate of soundness of sleep (5 = minimal, 18 = maximal night rating). The scatter diagram relating the total individual motility scores (10 p.m. to 6 a.m.), for each of the five nights to the ratings derived from the patients is depicted in Fig. 5, there being no significant correlation between the two ($r = +0{\cdot}04$, $P > 0{\cdot}15$).

Discussion

No one method used alone provides a satisfactory estimate of the hypnotic properties of drugs (Isaacs, 1957). However, the apparatus described above for recording movements during sleep or recumbency seems reliable and provides quantified data. The scores obtained were consistent if estimated over periods from 10 p.m. to either 2 a.m. or 6 a.m. Differences in mean motility scores that did emerge were ascribable to the differences between patients themselves rather than to discrepancies in serial functioning of the bed. As motility scores could be obtained at hourly intervals during the night, it was theoretically possible to study the time of onset of reduced movements, and, by inference, of the latency before significant drug action appears.

The apparatus required only weekly calibration and the incorporation of the valve and step-counter was a definite improvement. Small movements closely associated in time, but accompanied by subthreshold changes at the potentiometer, would

Please underline the answer you wish to give to the following questions concerning your sleep last night.

I got off to sleep in	(1) 15 minutes	(2) 30 minutes	(3) 45 minutes	(4) 60 minutes
I slept for	(5) 0-2 hours	(4) 2-4 hours	(3) 4-6 hours	(2) 6-8 hours	(1) longer than 8
My sleep was	(1) continuous	(2) broken once	(3) broken more than once	
My sleep was	(1) heavy	(2) sound	(3) light	
On waking I felt	(1) refreshed	(2) as usual	(3) tired	

Make any other comments in the space below:—

FIG. 5.—Scatter diagram of total motility scores (10 p.m. to 6 a.m.) and patients' rating for seven patients on five consecutive nights.

summate, which would have been impossible with the microswitch system on account of its inertia. However, as there is a slow leak of potential at the valve, intermittent small movements with spaced sub-threshold changes at the potentiometer will not summate. The other difficulty with the plunger and microswitch apparatus is that of the individual rolling on to his side and permanently depressing the microswitch, so creating a technical short circuit with no recording of further movement as long as he remains in that one position. This did not occur.

The high correlation between the nurses' rating of the patient's movement (and sleep) and the motility scores is striking, indicating that the apparatus was measuring restlessness. An objection could be that the rating of the patient's movement by one nurse and the recording of the appropriate motility score by another was not independent. The possibility of collusion, while feasible, is unlikely. Straus, Eisenberg, and Gennis (1955) relied on the nurses' estimation of the patient's sleep, regarding it as consistently superior to that of the patient.

There was no significant correlation between the patient's estimate of soundness of sleep and the motility scores. Two groups of investigators (Foltz, Dracos, and Gruber, 1955; Rushbrooke, Wilson, Acland, and Wilson, 1956) relied exclusively on the subjects' estimate of sleep. Imboden and Lasagna (1956) found there was a tendency for patients to underrate the effects of medication compared with the nurses' corresponding estimate.

One advantage of using motility as an index of sleep is that it is a continuous objective recording, in contrast to nurses' ratings of sleep which are subjective and intermittent. Little cooperation is required from the patient, a fact of importance if patients with psychiatric illnesses are included in the drug trial.

Summary

A method for measuring motility during sleep or recumbency is described.

Consistent results were obtained from one group of patients receiving placebo and from another taking either hypnotics or no medication.

Such differences in mean motility scores as did occur were ascribable to the differences between patients rather than to discrepancies in serial functioning of the apparatus.

The nurse's independent estimate of the patients' motility and sleep correlated highly with the motility scores.

The patient's estimate of the soundness of his own sleep did not tally with the motility scores.

We take pleasure in thanking Professor A. J. Lewis, whose suggestion it was to use motility as an index of sleep in psychiatric patients, Dr. D. L. Davies for his ready interest and encouragement, Dr. A. E. Maxwell for invaluable statistical advice, the nursing staff of Ward 4, particularly Sister H. Hynes and Nurse D. Hodge, and Mr. D. A. Green for photographing the stencils.

REFERENCES

Foltz, E. L., Dracos, F., and Gruber, C. M. (1955). *Amer. J. med. Sci.*, **230**, 528.

Hinton, J. M., and Marley, E. (1959). *J. Neurol. Neurosurg. Psychiat.*, **22**.

Imboden, J., and Lasagna, L. (1956). *Bull. Johns Hopk. Hosp.*, **99**, 91.

Isaacs, B. (1957). *Lancet*, **1**, 556.

Kleitman, N. (1932). *Proc. Soc. exp. Biol. (N.Y.)*, **29**, 389.

—— (1944). *Medical Physics*. Ed. O. Glasser. Vol. 1, p. 1433. Year Book Publishers, Chicago, Illinois.

Lasagna, L. (1954). *J. Pharmacol*, **111**, 9.

Maliniak, S. (1934). *Arch. psychol.*, **24**, 177.

Pai, M. N. (1950). *Recent Progress in Psychiatry*. Ed. G. W. T. H. Fleming, Vol. 2, p. 590. Churchill, London.

Rushbrooke, M., Wilson, E. S. B., Acland, J. D., and Wilson, G. M. (1956). *Brit. med. J.*, **1**, 139.

Straus, B., Eisenberg, J., and Gennis, J. (1955). *Ann intern. Med.*, **42**, 574.

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BLOOD-CEREBROSPINAL FLUID BROMIDE RATIOS IN MENTAL PATIENTS

BY

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"The fixity of the internal environment is in short the condition of mental activity." Barcroft (1934), by this modification of Claude Bernard's famous aphorism, emphasized the necessity of maintaining the constancy of the composition of the brain to ensure its normal functioning. Among the mechanisms for ensuring this constancy are the blood-brain and blood-cerebrospinal fluid barriers.

The term "blood-C.S.F. barrier" was first used by Stern (1923) and the concept was based on observations that the concentration of numerous substances in the blood and in the cerebrospinal fluid differed in such a way as to suggest a "barrier" between the two fluids. Many substances were used in studies of this barrier, notably sodium bromide whose many advantages were pointed out by Walter (1925). He found the ratio between the concentration of bromide in the cerebrospinal fluid and the concentration of bromide in the serum to be about constant, for any particular patient, when a steady state had been achieved.

The publication of Walter's observations was followed by the widespread use of bromide in the investigation of neurological and psychiatric disorders. The chief findings in the latter may be summarized as follows. Whereas the bromide ratio was normal in patients suffering from manic-depressive psychosis, schizophrenics had ratios indicating decreased permeability and patients with certain organic psychoses had ratios indicating increased permeability. There was considerable overlap between the ratios for the different groups, and the evaluation of the results remained equivocal because of the various criticisms which were levelled at the accuracy of the technique (*e.g.*, Fremont-Smith, Dailey, and Sloan, 1935; Carmichael, Rheingold, and Linder, 1935). It was thus desirable to repeat the work with a more accurate method. Such a method was provided by Hunter (1953).

The purpose of the present investigation was to see if mental diseases are associated with an alteration in the bromide ratio determined by Hunter's method.

Material and Methods

The diagnostic groups studied were: (*a*) Schizophrenia, (*b*) affective disorders, (*c*) senile psychosis, (*d*) puerperal psychosis, (*e*) general paresis. Altogether 79 patients were tested.

The ratios obtained from the patients were compared statistically with a control group. In a test involving a lumbar puncture it is hardly possible to obtain a random sample of healthy members of the general population. However, Drs. Honor Smith and George Hunter generously provided the clinical details and bromide ratios of 34 patients suffering from somatic complaints, in whom there was no evidence of mental illness or disease of the central nervous system. These patients formed the control group of the present investigation and will be described in detail later. The psychiatric subjects were patients in whom the diagnosis was unequivocal and had been confirmed by at least one consultant psychiatrist. To avoid the possible effects of deep insulin and electro-convulsive therapy on the bromide ratio, no patient was included who had had physical treatment during the year preceding the test.

Sodium bromide was administered orally for three days in a dose of 1 g. thrice daily. Two days were then allowed to elapse and on the sixth day cerebrospinal fluid was obtained by lumbar puncture with the patient lying in the right lateral position. Approximately 5 ml. of fluid was obtained by direct flow into a chemically clean container. About 10 ml. of blood was obtained by venepuncture within 30 minutes of the lumbar puncture. The blood was allowed to clot and was centrifuged to separate cells and serum.

The reliability of the bromide estimations was investigated by calculating the product moment correlation coefficient between the duplicate results of the first 20 estimations. The correlation coefficient was high (0·98) indicating a very satisfactory level of reliability for the test both in blood and cerebrospinal fluid.

Results

The mean and standard deviation of the bromide ratio and the age of the patients of the control and the other groups are given in Table 1. Comparisons of the bromide ratios between the various groups by the t test are shown in Table II.

TABLE I

BROMIDE RATIOS AND AGES OF THE CONTROL AND PSYCHIATRIC GROUPS

Group	No.	Age		Bromide Ratio		Correlation Coefficient for Age and Bromide Ratio
		Mean	S.D.	Mean	S.D.	
Control	34	42·7	20·2	0·39	0·06	0.41 $P < 0.02$
Schizophrenia	27	31·4	7·8	0·40	0·07	0·10 not significant
Affective disorders	17	40·9	11·3	0·39	0·05	0·55 $P < 0.05$
Senile dementia	17	72·6	3·4	0·42	0·06	0·28 not significant
Puerperal psychosis	10	29·7	3·0	0·38	0.06	0·49 not significant
General paresis	8	56·0	14·2	0·37	0·03	0·54 not significant

TABLE II

COMPARISON OF BROMIDE RATIOS OF VARIOUS PSYCHIATRIC GROUPS WITH CONTROL GROUP AND EACH OTHER BY t TEST

Groups Compared	t	P
Schizophrenia: control	0.44	Not significant
Schizophrenia: affective disorder	0.36	Not significant
Schizophrenia: senile psychosis	1.13	Not significant
Affective disorder: control	0	Not significant
Affective disorder: senile psychosis	1.55	Not significant
Senile psychosis: control	1.79	Not significant
Puerperal psychosis: control	0.30	Not significant
Puerperal psychosis: schizophrenia	0.57	Not significant
General paresis: control	0.95	Not significant
General paresis: senile psychosis	2.23	0.05

Control Group.—This consisted of 34 patients with the following diagnosis, the number of patients in each category being given in brackets: (*a*) Glaucoma (6); (*b*) tuberculosis without meningitis (11); (*c*) pain referred to various parts of the body, namely, the face (2), the head (8), the arm (2), and the leg (1); (*d*) myxoedema (4).

Schizophrenia.—Some of the patients tested had had schizophrenia for many years, in others the illness was of recent onset. The bromide ratios of the latter were substantially the same as those of the chronic patients. The group consisted of 27 patients, 18 of whom were hebephrenic, three catatonic, five showed simple schizophrenia, and one paranoid schizophrenia.

Affective Disorders.—This group consisted of 17 patients suffering from depression.

Senile Dementia.—There were 17 in this group. Patients with evidence of cerebral arterial disease, such as cerebrovascular lesions, hypertension, and a markedly fluctuating or remitting course were excluded.

Puerperal Psychosis.—This group consisted of 10 women who became severely mentally disturbed in the course of their puerperium. Nine of them presented a schizophrenic-like picture, one presented with depressive features. They were tested within one month of the onset of symptoms.

General Paresis.—This group consisted of seven patients with treated general paresis and one with juvenile paresis in whom there were residual mental symptoms necessitating a continued stay in hospital. The diagnosis had been established in every case by serological and cerebrospinal fluid investigations.

There was no significant difference between the bromide ratios of the psychiatric groups when compared with each other or with the controls except in the case of patients with general paresis, who had lowered bromide ratios. A positive correlation was found between age and bromide ratio in the controls and in patients with affective disorders.

Discussion and Conclusions

The results of this investigation indicate that, with the exception of the general paresis group, none of the psychiatric patients had bromide ratios that differed significantly from the control group.

The discrepancy between these results and those of previous workers is not easily explained. It cannot be entirely accounted for by inaccuracies in their technique of estimating bromide. A more important source of error would be that they performed the test on the day following the administration of bromide. As Hunter, Smith, and Taylor (1954) showed, this is too short a time for the steady state to be reached. It is therefore possible that the difference they reported between the groups of mental patients is related to an abnormal rate of penetration of bromide into the cerebrospinal fluid rather than to an abnormal steady state distribution. Rates of penetration of bromide have not been systematically measured in mental patients, but there is some evidence that the reverse process, *i.e.*, the penetration of sodium iodide from the cerebrospinal fluid into the blood is abnormal in schizophrenics. This was found by Guttmann (1929). He used Foerster's (1925) test, in which 2 ml. of 10% solution of sodium iodide is injected into the lumbar subarachnoid space and the excretion of iodide is studied in the urine; in normal conditions the iodide appears in the urine within 30 to 45 minutes of the injection, and the duration of iodide excretion is regarded as normal up to 35 hours from its injection into the cerebrospinal fluid. In 50 schizophrenics Guttmann found that 36 showed a delayed excretion of up to seven hours and 14 an abnormally long duration of iodide

excretion; only nine showed a normal iodide excretion.

The low bromide ratio observed in the general paretic group is also difficult to account for in contrast to the increased permeability found by earlier workers, except that this was with untreated cases. Kral (1928) and Malamud and Wilson (1929) reported that patients who had been given malaria therapy and improved showed a change from increased to normal permeability.

The control group and the group of affective disorders show a significant positive correlation between age and bromide ratio, and this confirms similar findings by Büchler (1926), Carmichael *et al.* (1935), and Bourdillon, Fischer-Williams, Smith, and Taylor (1957). In contrast to these two groups, the bromide ratios of the schizophrenic patients do not show a correlation with age. The small numbers and limited age range of the groups of senile dementia, puerperal psychosis, and general paresis are probably a sufficient reason why a positive correlation between age and bromide ratio did not emerge from these groups.

The present work shows that the steady-state bromide ratio is unchanged in mental patients, but it would be rash to conclude from this that the blood-brain and blood-cerebrospinal fluid barriers are normal in these patients. As Davson (1956) demonstrated, permeability is best measured by determining the rate of penetration of a substance from one side of a membrance to another, rather than by measuring the steady-state ratio. Thus Bourdillon *et al.* (1957) found a decreased rate of penetration of bromide and sodium into the cerebrospinal fluid in patients with extrapyramidal lesions, although the steady-state ratios of these substances were normal.

Summary

An accurate method of determining the bromide content of serum and cerebrospinal fluid was applied to a study of the permeability of the blood cerebrospinal fluid barrier in mental patients. The diagnostic groups investigated were (*a*) schizophrenia, (*b*) affective disorders, (*c*) senile dementia, (*d*) puerperal psychosis, (*e*) general paresis, and the findings were compared with those in a control group of patients without any mental disorder or disease of the central nervous system. The bromide ratios in schizophrenia, senile dementia, affective disorders, and puerperal psychosis do not differ from those in patients not suffering from mental illness. Patients suffering from general paresis had a slightly decreased bromide ratio.

I should like to thank Dr. Honor Smith and Dr. George Hunter for generously providing the bromide ratios of the control group.

References

Barcroft, J. (1934). *Features in the Architecture of Physiologica Function.* Cambridge University Press, London.
Bourdillon, R. B., Fischer-Williams, M., Smith, Honor V., and Taylor, K. B. (1957). *J. Neurol. Neurosurg. Psychiat.*, **20**, 79.
Büchler, P. (1926). *Arch. Psychiat. and Nervenkr.*, **77**, 613.
Carmichael, H. T., Rheingold, J. C., and Linder, F. E. (1935). *J. nerv. ment. Dis.*, **82**, 125.
Davson, H. (1956). *Physiology of the Ocular and Cerebrospinal Fluids.* J. & A. Churchill, London.
Foerster, O. (1925). *Z. ges. Neurol. Psychiat.*, **94**, 512.
Fremont-Smith, F., Dailey, M. E., and Sloan, D. H. (1935). *Arch. Neurol. Psychiat. (Chicago)*, **33**, 764.
Guttmann, L. (1929). *Arch. Psychiat. Nervenkr.*, **88**, 211.
Hunter, G. (1953). *Biochem. J.*, **54**, 42.
——, Smith, H. V., and Taylor, L. M. (1954). Ibid., **56**, 588.
Kral, A. (1928). *Z. ges. Neurol. Psychiat.*, **115**, 158.
Malamud, W., and Wilson, R. B. (1929). *Arch. Neurol. Psychiat. (Chicago)*, **22**, 1135.
Stern, L. (1923). *Schweiz. med. Wschr.*, **4**, 792.
Walter, F. K. (1925). *Z. ges. Neurol. Psychiat.*, **95**, 522.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 64.

AN ANGIOGRAPHIC TEST OF COLLATERAL CIRCULATION THROUGH THE ANTERIOR SEGMENT OF THE CIRCLE OF WILLIS

BY

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This communication is concerned with the angiographic estimation of collateral circulation through the anterior segment of the circle of Willis. The collateral circulation, which may be present between the ophthalmic artery and the branches of the external carotid artery and the posterior segment of the circle of Willis carrying blood from the vertebral circulation, is outside the scope of this discussion.

This angiographic test of the collateral circulation has been carried out sporadically in neurosurgical services all over the world. Personal experience of it extends over 13 years.

The estimation of its adequacy through the anterior cerebral arterial complex is of great practical importance to neurosurgeons if it is proposed to treat certain intracranial aneurysms by ligating the internal carotid artery or the anterior cerebral artery. In recent years general physicians and neurologists have been interested in its role, as spontaneous or traumatic thrombosis of the internal carotid artery has become a well established diagnosable entity. The many and variable clinical symptoms and signs of that condition (which is sometimes symptomless) can be largely explained by the anatomical and dynamic state of the collateral circulation through the anterior segment of the circle of Willis. Other possible collateral channels may also be brought into play later.

The stimulus to employ this angiographic test in a larger number of patients was provided by the observation that some elderly subjects possessed an excellent collateral circulation. Two questions were posed: (1) Can angiography substantiate or refute the belief that collateral circulation deteriorates with age so that thrombosis or ligation of the internal carotid artery becomes excessively hazardous after the age of 50 ? (2) To what extent can the collateral circulation be disturbed by other factors ?

In an attempt to elucidate the answer to these questions, the test was performed on patients subjected to diagnostic angiography in the Regional Neurosurgical Centre at Liverpool from 1954 to 1957. At first digital compression was carried out on each case.

Unfortunately at the beginning of 1956 the two surgeons carrying out this experiment were warned that dangerous amounts of radiation were being received on their hands. In view of this the routine performance of the test was discontinued. Thus only 712 patients had the collateral circulation tested.

The view held here is that angiography is the safest method of investigation in cerebral contrast radiography. Its technique and the reasons why it is considered safe have been discussed at length in a previous communication (Sedzimir, 1955). The series is now close to 2,000 angiograms without death, with one case of transient hemiparesis, two transient supranuclear facial palsies, and one case of infection of the neck which resolved without surgical intervention.

Technique of Test

All angiography was performed under general anaesthesia. Contrast medium was injected into one carotid artery just below the carotid sinus by the percutaneous method. A few seconds before the start of the injection, the opposite internal carotid artery was digitally compressed. Three exposures in the antero-posterior projection were made. Frequently a bilateral estimation was carried out at the same sitting.

Definitions

For the purpose of this experiment it was arbitrarily defined that collateral circulation through the anterior segment of the circle of Willis was classified as:

(1) " Good " if in addition to the ipsilateral arteries, the contralateral anterior and middle cerebral arteries were filled (Fig. 1).

(2) " Poor " if the contralateral anterior cerebral artery was filled, the contrast medium not entering the contralateral middle cerebral artery (Fig. 2).

(3) " Absent " if only the ipsilateral middle cerebral artery, or the ipsilateral middle and anterior cerebral arteries were visualized (Figs. 3 and 4).

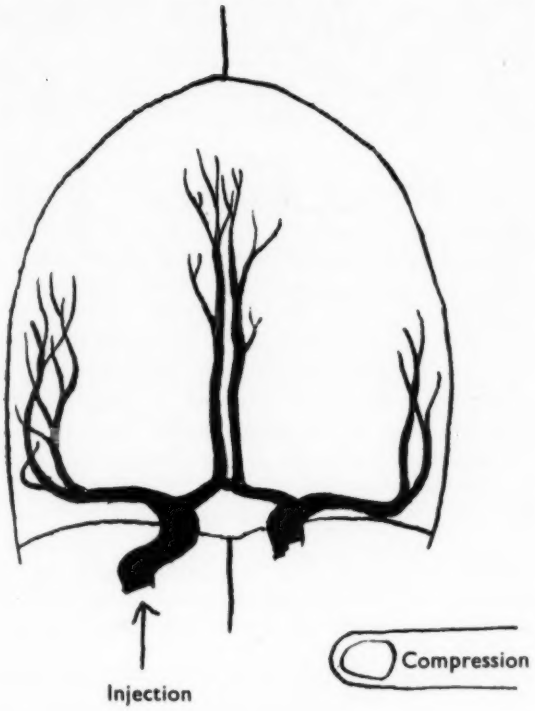

FIG. 1

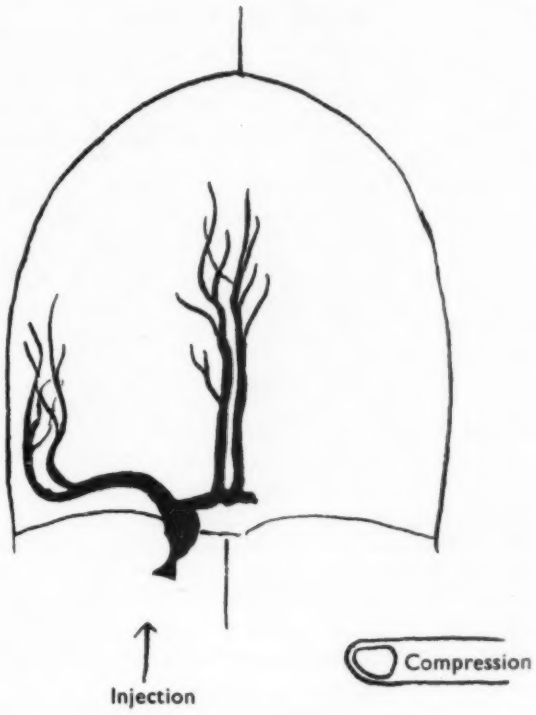

FIG. 2

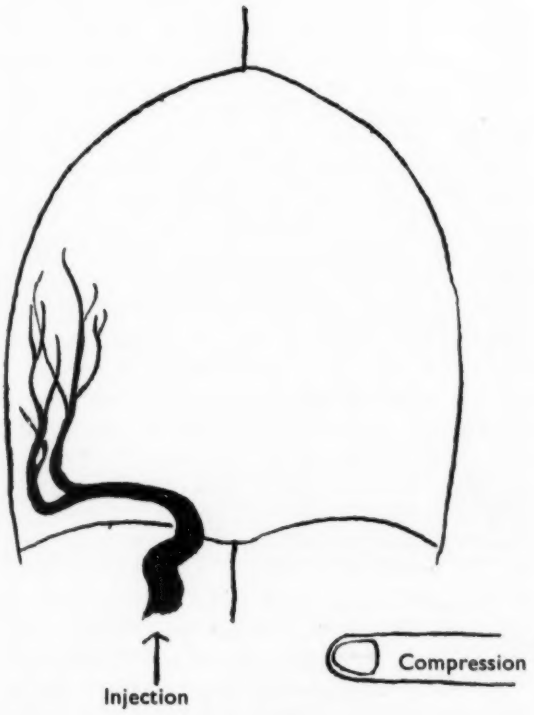

FIG. 3

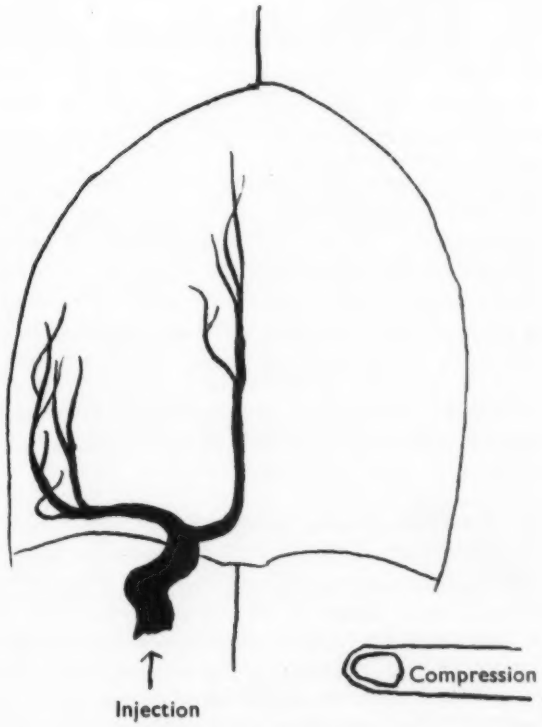

FIG. 4

Results and Discussion

In a high proportion of cases of "absent" or "poor" collateral circulations, besides carrying out the test bilaterally, a second and even a third estimation was performed at intervals of a few days to five to six weeks.

Only in 14 patients was the collateral circulation found to be different when tested on separate occasions and only these are included twice in the total number of the tests. For this reason it is stated that in 712 patients the number of collateral circulations tested was 726, though in fact it was a much larger number.

Of the 726 tests (Table I), in 52 the collateral circulation was "absent" (7·1%); in 171 it was "poor" (23·6%); and in 503 it was "good" (69·3%).

TABLE I

STATE OF COLLATERAL CIRCULATION IN 712 PATIENTS

Total no. of patients	712	
Total no. of collateral circulations tested	726	
Good	503	(69·3%)
Poor	171	(23·6%)
Absent	52	(7·1%)

Grouping together all the "vascular conditions" (Table II), there were 364 patients in whom 378 tests were performed. Of these, 31 (8·2%) were defined "absent", 87 (23%) "poor", and 260 (68·8%) "good" (Table III). The difference between this group and the overall numbers is trifling.

TABLE II

VASCULAR CONDITIONS

Bleeding aneurysms	155
Subarachnoid haemorrhage, aetiology not disclosed on angiography	126
Bleeding arteriovenous anomaly	33
Massive cerebral haemorrhage, aetiology not disclosed on angiography	5
Non-bleeding aneurysm or arteriovenous anomaly	11
Arterial thrombosis	33
Total	363

TABLE III

STATE OF COLLATERAL CIRCULATIONS RELATED TO VASCULAR CONDITIONS

Vascular Conditions		
No. of patients	364	
No. of collateral circulations tested	378	
Good	260	(68·8%)
Poor	87	(23%)
Absent	31	(8·2%)

On the other hand it was only in this particular group that in 14 patients the collateral circulation was found different when tested on separate occasions. They constitute approximately 4% of the vascular cases and 2% of the overall numbers.

The conditions in which the test was performed in the remaining 348 patients are shown in Table IV. The collateral circulation was found to be absent in 21 (6%), poor in 84 (24%), and good (Table V) in 243 (70%).

TABLE IV

CONDITIONS OF TEST IN REMAINING PATIENTS

Tumours	120
Epilepsy	67
Degenerative	37
Head injury	13
Chronic subdural haematoma	7
Migraine	15
Miscellaneous	89
Total	348

TABLE V

STATE OF COLLATERAL CIRCULATION IN NON-VASCULAR CONDITIONS

Non-vascular Conditions		
No. of collateral circulations tested	348	
Good	243	(70%)
Poor	84	(24%)
Absent	21	(6%)

Once again it is evident that there was only an insignificant difference of the percentages of absent, poor, and good collateral circulations between the non-vascular and vascular conditions as well as the overall numbers (cf. Tables I, II, and V).

The analysis of the influence of age on the anatomical channels of collateral circulation across the anterior cerebral complex occasioned the greatest surprise.

Of the total of 726 tests, 516 fell in the age groups 1-49 years inclusive (the youngest patient was 6 months old). In 37, the collateral circulation was absent (7·2%), in 122 was poor (23·6%), and in 357 (69·2%) was good. Two hundred and ten tests were performed in the age group 50-70+ (the oldest patient was 74). In 15 (7·1%), it was absent, in 49 (23·3%) it was poor, and in 146 (69·6%) it was good (Table VI).

TABLE VI

STATE OF COLLATERAL CIRCULATION RELATED TO AGE

Age 0-49		Age 50-70+	
No. of tests	516	No. of tests	210
Good	357 (69·2%)	Good	146 (69·6%)
Poor	122 (23·6%)	Poor	49 (23·3%)
Absent	37 (7·2%)	Absent	15 (7·1%)

Evidently there is no real difference between the collateral circulation across the anterior segment of the circle of Willis in the under-50s and the over-50s. These percentages are, in turn, practically identical with the findings obtained by analysis of the aetiological groups.

It was thought unimportant to work out statistics for subdivisions of the aetiological conditions enumerated in Tables II and IV or to subdivide the ages into decades. The small numbers of tests in each such subdivision would make any statistical analysis impracticable.

Poor collateral circulation was found in this series to be in the order of 23 to 24%, irrespective of age or pathology. Compression of the opposite internal carotid artery was digital and percutaneous. It is, therefore, conceivable that a proportion of this percentage was the result of an inefficient compression. Thus, what may have been cases of good collateral circulation became poor, according to the adopted definition, and this may have occurred in ±10% of tests. In another, as yet indefinite percentage, the primary source of collateral circulation was presumably through the posterior segment of the circle of Willis. A full experimental study is still needed here.

Finally, some cases classified in this group were due to the dynamic influences which are less generally appreciated but have been discussed by some authors (Sweet and Bennett, 1948; Shenkin, Harmel, and Kety, 1948; Shenkin, Cabieses, van den Noordt, Sayers, and Copperman, 1951; Stern, 1953; Strobos and Mount, 1953; Brown, 1955).

The circle of arterial channels at the base of the brain known to us as the circle of Willis was recently the subject of an admirable review by Sir Charles Symonds (1955). The anterior segment of this circle comprises the supraclinoid segment of the two internal carotid arteries, proximal segments of the anterior cerebral arteries which are joined together by the anterior communicating artery. This arterial complex may be defective as a result of a congenital abnormality. It may take the form of an absent, or grossly underdeveloped anterior communicating artery or a similar condition involving the proximal segment of one anterior cerebral artery. When this last anomaly is present the arteriographic appearance or the post-mortem anatomical dissection shows the two anterior cerebral arteries as an integral system of one internal carotid artery. The other internal carotid artery has as its main branch the middle cerebral artery. It then takes no part in the formation of the anterior segment of the circle of Willis. The collateral circulation in such cases is absent, but the angiographic test must be performed bilaterally and repeated at a second investigation. When these criteria were fulfilled only a very few cases of such an anomaly were proved, and usually though not exclusively in the presence of an aneurysm of the anterior cerebral arterial complex. This combination is well known although sometimes overemphasized.

As stated previously, in the groups of patients with vascular pathology there were 14 out of 364 in whom different results were obtained when the test was performed on separate occasions (4%). The reason for the alterations was segmental spasm affecting the part of the circle under discussion. All these were cases of intracranial bleeding from a verified aneurysm subjected to angiography from a few hours to a few days after the haemorrhage. The test was repeated at intervals varying from a few days to three weeks. In each of these patients an absent or poor collateral circulation became poor or good accordingly. Although the patients with arterial anomalies and arterial spasm represent only a small percentage of the vascular cases, they must be taken into careful consideration when contemplating surgical treatment of intracranial haemorrhage. It was felt important to draw attention to these cases. Moreover, having done so, it is reemphasized that absent collateral circulation was found in 31 patients (8·2%) in this group. In the groups comprising all other pathological conditions, there were 21 (6%) patients out of 348. The difference of 2·2% is of no great significance in a series of this size.

The limitations of this angiographic experiment must be acknowledged, since it can never be an absolutely true image of the circulation. The lack of an apparatus in this Centre which would allow taking more than three exposures is highly regretted. Despite these reservations, it is felt that the most interesting finding in this series is the apparent refutal of the common belief that age materially affects the collateral circulation through the circle of Willis. It may be that in younger age groups bleeding conditions and anatomical anomalies play a greater part, whereas in the older groups dynamic influences predominate as factors affecting the collateral circulation. It is also true that there were 516 patients in the group of under 50 years of age and only 210 in the group over 50. Nevertheless, in the former group collateral circulation was absent 7·2% (37 times), poor 23·6% (122 times), while in the latter it was absent in 7·1% (15 times) and poor in 23·3% (49 times) (Table VI). These percentages are identical and it is felt that they cannot be disregarded.

Under the conditions of this experiment, the anterior segment of the circle of Willis seemed anatomically and dynamically an admirable device for the carriage of the blood supply in health and its redistribution in stress.

Summary

An angiographic test estimating the collateral circulation through the anterior segment of the

circle of Willis has been carried out in 712 patients.

The results were analysed in relation to age and pathology.

REFERENCES

Brown, A. S. (1955). *Anaesthesia*, **10**, 346.
Sedzimir, C. B. (1955). *J. Neurosurg.*, **12**, 460.
Shenkin, H. A., Harmel, M. H., and Kety, S. S. (1948). *Arch. Neurol. Psychiat.* (*Chicago*), **60**, 240.
——, Cabieses, F., Noordt, G. van den, Sayers, P., and Copperman, R. (1951). *J. Neurosurg.*, **8**, 38.
Stern, W. E. (1953). *Ibid.*, **10**, 577.
Strobos, R. R. J., and Mount, L. A. (1953). *A.M.A. Arch. Neurol. Psychiat.*, **69**, 118.
Sweet, W. H., and Bennett, H. S. (1948). *J. Neurosurg.*, **5**, 178.
Symonds, Sir Charles (1955). *Brit. med. J.*, **1**, 119.

THE NOVEMBER (1958) ISSUE

The November (1958) issue contains the following papers:—

Further Observations on Subarachnoid Haemorrhage. Wylie McKissock, Kenneth Paine, and Lawrence Walsh

Leucotomy for Pain. Alick Elithorn, Eric Glithero, and Eliot Slater

A Controlled Study of the Effects of Leucotomy. A. A. Robin

Thyrotoxic Myopathy. Ragnar Hed, Lennart Kirstein, and Curt Lundmark

Individual Variation in the Size of the Tentorial Opening. J. A. N. Corsellis

Arteries of the Spinal Cord in the Cat. Peter Bradshaw

Accommodation in the Holmes-Adie Syndrome. G. F. M. Russell

The Effect of Reserpine on the Duration of Manic Attacks. David C. Watt

A Controlled Trial of Meprobamate in Anxious Out-Patients. John M. Hinton

Myeloid Cells in Cerebrospinal Fluid. A. I. Spriggs

Two Hundred and One Cases of Intracranial Tuberculoma Treated Surgically. C. Arseni

Book Reviews

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J. Neurol. Neurosurg. Psychiat., 1959, **22**, 69.

THE APPLICATION IN GENERAL MEDICAL CONDITIONS OF A VISUAL METHOD OF ASSESSING AND REPRESENTING GENERALIZED ELECTRO-ENCEPHALOGRAPHIC ABNORMALITIES

BY

JOHN LAIDLAW

From the Department of Medicine : Neurology, Postgraduate Medical School, London

Certain disorders, which do not primarily involve the brain, may interfere with its metabolism. If this metabolic dysfunction is sufficiently severe the patient may become confused or even comatose. The continuum from normality to coma will here be considered as one of increasing delirium. Such delirium may be produced by a variety of conditions which include those with alterations in blood chemistry, namely, hypoglycaemia, uraemia, and possibly hypokalaemia (Sherlock, Read, Laidlaw, and Haslam, 1958); certain of the collagen diseases (Leinwand, Duryee, and Richter, 1954; Clark and Bailey, 1956); pernicious anaemia (Walton, Kiloh, Osselton, and Farrall, 1954; Holmes, 1956); carbon dioxide narcosis complicating chronic bronchitis and emphysema (Westlake and Kaye, 1954; Conn, Dunn, Newman, and Belkin, 1957); and those forms of liver disease associated with encephalopathy (Adams and Foley, 1953; Summerskill, Davidson, Sherlock, and Steiner, 1956).

The electroencephalogram (E.E.G.) can define the extremes of this continuum. At one end, the wide range of normal is characterized by rhythmic activity predominantly within the alpha frequency band (8-13 c./sec.) and at the other, coma by delta waves (under 4 c./sec.) of varying regularity and amplitude.

In the zone between, however, the E.E.G. changes are less clear. It is very difficult by inspection to assess variations in the severity of a generalized abnormality and even more difficult to express such an assessment, except as an arbitrary statement of opinion. Not only is a method of assessment essential for any E.E.G. investigation of delirium but it is of practical clinical importance to be able to detect relatively small changes, and to have a language in which to explain them. First, because the E.E.G. provides an objective and often sensitive index of cerebral function and ought to be able to help by warning of clinical deterioration or measuring the efficacy of treatment. Secondly, because although the E.E.G. changes in disorders not primarily cerebral, such as those described, are not specific, the E.E.G. can help in diagnosis if it is possible to measure the effect of provocative or therapeutic tests.

This paper describes a method which has been developed to assist in the assessment and representation of such generalized abnormalities. Work on the E.E.G. during the transition from consciousness to coma is in progress and definitive results have not yet been obtained. Some description of this work is given and tentative hypotheses mentioned in order to clarify the scope and limitations of the method.

A number of patients, the majority with liver disease, have been followed with daily E.E.G.s as they recovered from or lapsed into coma or states of manifest confusion. Inspection of the records suggested:

(1) That the changes which occurred were not specific to any disease.

(2) That the most important change, with increasing delirium, was a slowing of frequency both as a slowing of the dominant frequency and as the introduction of random slow waves.

(3) That variations in the amount of rhythmic activity, particularly with the eyes open, were probably important.

(4) That during certain stages of delirium there were considerable intra-record variations which occurred both spontaneously and as a result of stimuli intended to influence the patient's state of attention.

(5) That slowing was usually seen first over the lateral and post-central parts of the scalp, and that although with advancing delirium very slow waves might be maximal anteriorly, if a single area of the scalp needed to be chosen for inspection, the postero-lateral aspect of the non-dominant hemisphere gave the most satisfactory measure of the frequency changes over the whole spectrum of delirium.

The method was developed in order to quantitate and express graphically changes which had been

observed and which were considered to be associated with alterations in delirium. It was decided not to use an automatic frequency analyzer for two main reasons: (1) The apparatus, which is expensive and requires skilled maintenance, is seldom available outside special centres, and a method to be of use must be available in those units where general medical cases are found. (2) The present analyzers only record the energy at different frequencies, *i.e.*, the product of amplitude (voltage) and number of waves. Frequency changes were considered of primary importance and it was felt that more weight should be given to a large number of moderate amplitude waves than to a smaller number of high amplitude ones. Further, a measure was required of the ratio of rhythmic activity to irregular and desynchronized parts of the record.

In 1944, Engel, Romano, Ferris, Webb, and Stevens described a simple visual method of frequency analysis. They counted the number of complete waves in each of 300 consecutive one-second periods, excluding those containing low-voltage fast activity, expressing the result as a histogram. A recent application of this method showed the E.E.G. effects of alcohol (Holmberg and Martens, 1955).

The method to be described is a development of Engel's and similar to one used by Brazier and Finesinger (1944) to study the normal E.E.G. It attempts to overcome, first, the disadvantage of forming a histogram from averages and so masking the occurrence of frequencies far removed from the mean and failing to give a measure of the degree of polyrhythmia, and secondly, the difficulty of dealing with irregular records and those containing a high proportion of low-amplitude fast activity. It must be emphasized that although it deals with frequencies and expresses them in mathematical and graphical form, it should not be thought of as a method of frequency analysis in the sense that an automatic analyzer analyses frequency, but as a way of representing a generalized abnormality as a frequency pattern.

Method

Essentially, the principle is to measure the periods of as many individual waves as possible over a given epoch* to calculate the time occupied by each frequency, and to plot on a graph the frequency-time as a percentage of the epoch, against frequency, to give a frequency pattern (Fig. 4).

Scalp electrodes are placed as shown in Fig. 1 to give seven channels of E.E.G. The spare channel of an eight-channel machine may be used for other purposes such as an electrocardiograph lead or the recording of alerting stimuli. It has been found that the best measure of frequency changes is given from the postero-lateral aspect of the non-dominant hemisphere (channel 5 for a right-handed patient). Time constants of 0·3 sec. are suitable and have been used throughout in the work described.

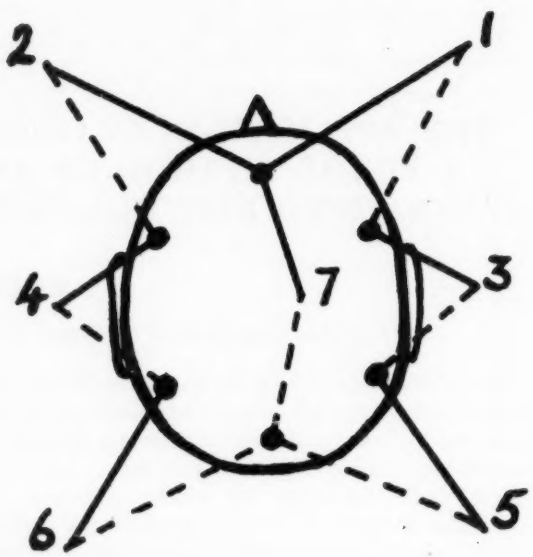

FIG. 1.—Position of scalp electrodes and connexions of seven E.E.G. channels.

All rhythmic and reasonably regular waves are counted. Certain parts of each epoch are excluded according to the following criteria.

(1) Those which are flat and desynchronized: with amplitude calibration at 1 cm. for 50 microvolts and paper speed of 6 cm. per second, a wave is considered flat if its height is less than a quarter of its width. If all the rhythmic activity in a record is of low amplitude this criterion may be modified.

(2) Very irregular activity when it is impossible to define a wave clearly. In practice very little of an epoch needs to be left out for this reason.

(3) Activity with a frequency above 20 c./sec. which is uncommon in the records which have been considered.

Only the wave which is dominant at any one time is measured. Thus a low-amplitude ripple superimposed on a large slow wave is ignored. It is usually quite easy to decide which wave form should be counted, but if there is difficulty, activity recorded simultaneously in other channels is considered.

The period of each wave, from trough to trough, is measured with the cursor shown in Fig. 2. The numbers at the top of the cursor give the frequency when the paper is run at the normal speed of 3 cm./sec. Unless the record consists of predominantly delta activity, measuring is easier if the gains are doubled and the paper run at 6 cm./sec.; at this speed the frequencies are given by doubling the numbers at the top of the cursor. The intervals between the measuring lines on the cursor

*Although not strictly correct etymologically the word "epoch" can be used with advantage to mean "a period of time".

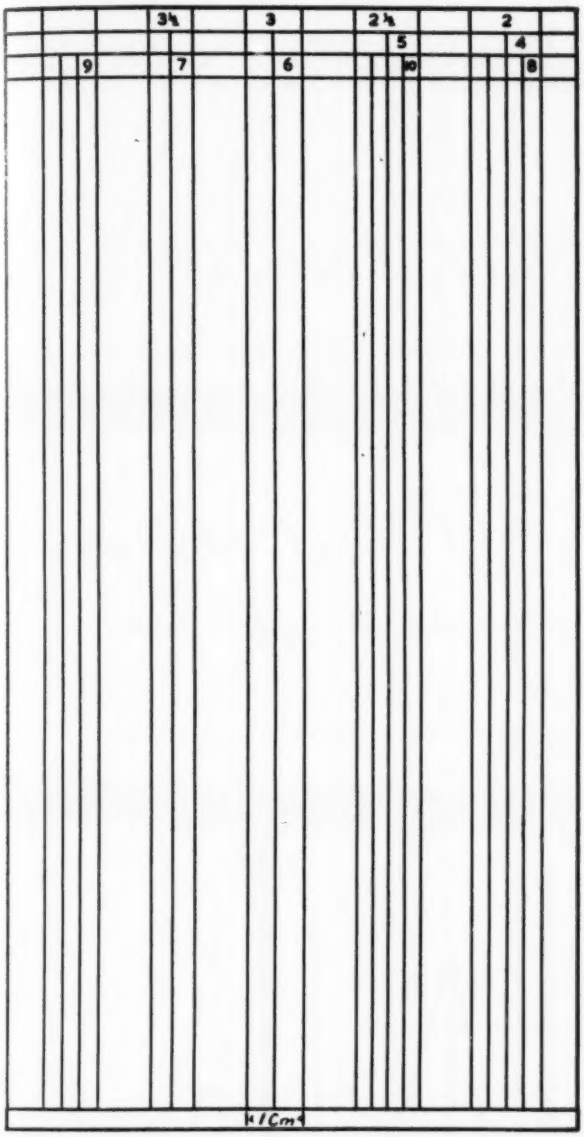

FIG. 2.—Cursor used for measuring periods of waves. The figures at the top indicate the frequencies when the paper speed is 3 cm./sec.

are each 1 cm. and very slow waves can be measured by making an appropriate combination of measuring line and interval, *e.g.*, the measuring line for 3 with the intervals on either side of it measure 3 cm. and at 6 cm./sec. represent a wave at 2 c./sec.

Over the continuum from normal consciousness to coma, records tend to show a considerable variation from one part to another (part B in Fig. 3) and it is usually necessary to measure an epoch of 50 seconds. At the extremes of the continuum of delirium, where there tends to be less variation, the epoch may be shorter. If it is decided to attach significance to a certain degree of change in the frequency pattern, it is necessary to choose an epoch long enough so that if two epochs of this length are counted from the same record under similar circumstances, *i.e.*, with the eyes shut or open, the variation between the frequency patterns from these epochs is appreciably less than the change to which significance is to be attached.

In most cases an epoch can be measured without any preparation and the frequencies called out to an assistant or a tape recorder; with practice a 50-second epoch can be measured in about 10 minutes. As a refinement (and for difficult records) it is sometimes useful to mark doubtful parts of an epoch with vertical pencil lines through the troughs of waves before measuring. This saves time in the end and allows a colleague to check. Fig. 3 shows examples of a normal record (*A*), a moderately abnormal record (*B*) from a patient, who although showing no clinical evidence of delirium, was in fact deteriorating and later became manifestly confused, and a severely abnormal record (*C*) from a patient in coma. The frequencies have been written in below the waves; those parts without subscripted numbers have been excluded according to the criteria given.

The number of waves at each frequency divided by the frequency gives the time occupied by that frequency. If a 50-second epoch has been measured, this time multiplied by 2 gives the frequency-time per cent. Since it is difficult, and not sufficiently important, quickly to differentiate frequencies over 10 c./sec. the faster waves are grouped together: those from 11 to 13 c./sec. as 11/13 and from 14 to 20 c./sec. as fast. When calculating frequency time these groups are divided by 12 and 15 respectively and are plotted on the frequency pattern as blocks not points.

Fig. 4 shows the frequency patterns derived from the records, of which specimens are shown in Fig. 3. It will be seen that whereas the patterns for the normal (*A*) and severely abnormal (*C*) records show sharp peaks with most of the activity at one or two frequencies, the moderately abnormal (*B*) pattern is more broadly based, demonstrating the polyrhythmia and intra-epoch fluctuation which was seen in Fig. 3 *B*.

Illustrative Material

Examples from two sets of serial records are shown in Figs. 5, 6, and 7. Specimens of the original E.E.G.s are seen to the left (the numbers referring to the channels marked in Fig. 1) and the corresponding frequency patterns on the right are each derived from 50-second epochs with the eyes shut. The area under the frequency pattern gives a measure of the amount of rhythmic activity, the time occupied by the rhythmic and reasonably regular waves which have been counted.

Figs. 5 and 6 (Case 1) show E.E.G.s recorded on six consecutive days from a patient with cirrhosis complicated by encephalopathy. At the time of the first record (*A*) she was manifestly confused. Five days later (*F*) she had returned to her usual state. The following points may be noted:

(1) There is a gradual increase in frequency throughout the series.

(2) Even after recovery from the acute episode there is a slight generalized abnormality as shown by an excess of activity at frequencies less than 8 c./sec.

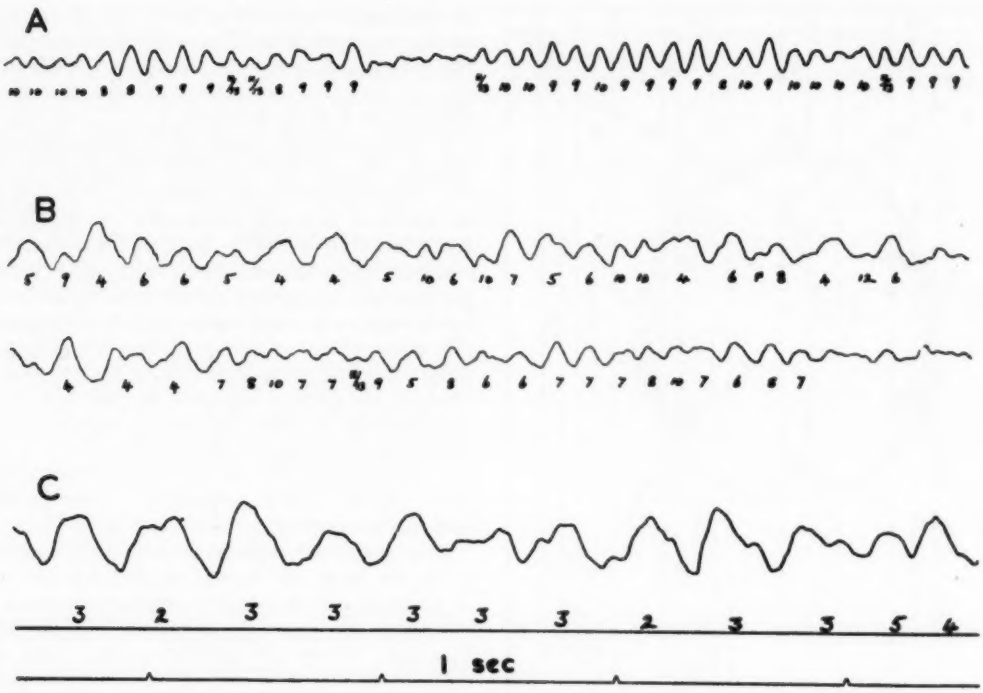

FIG. 3.—Specimens of a normal (*A*), moderately abnormal (*B*), and severely abnormal (*C*) record. The frequencies of those waves which have been counted are subscripted.

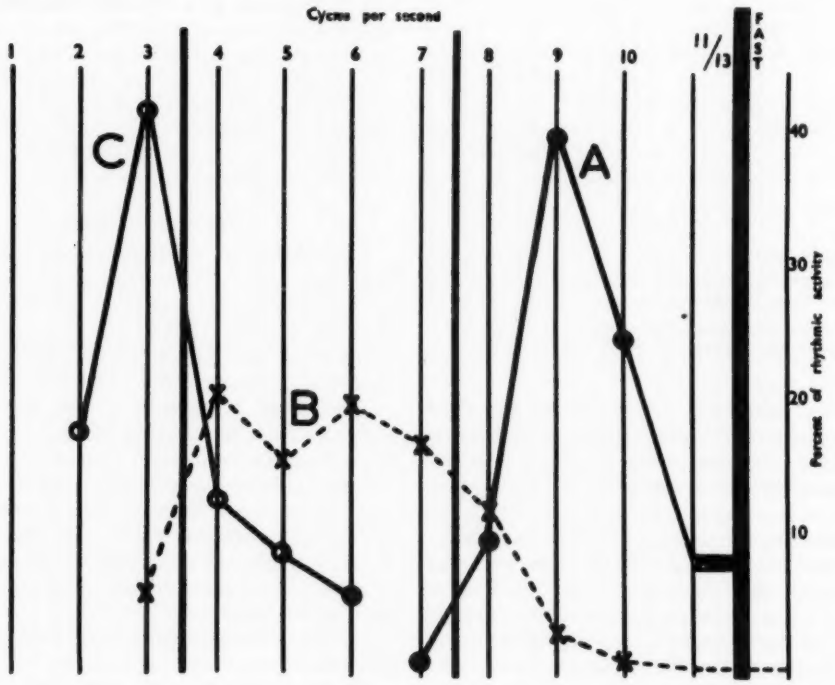

FIG. 4.—Frequency patterns of the normal (*A*), moderately abnormal (*B*), and severely abnorma (*C*) records shown in Fig. 3.

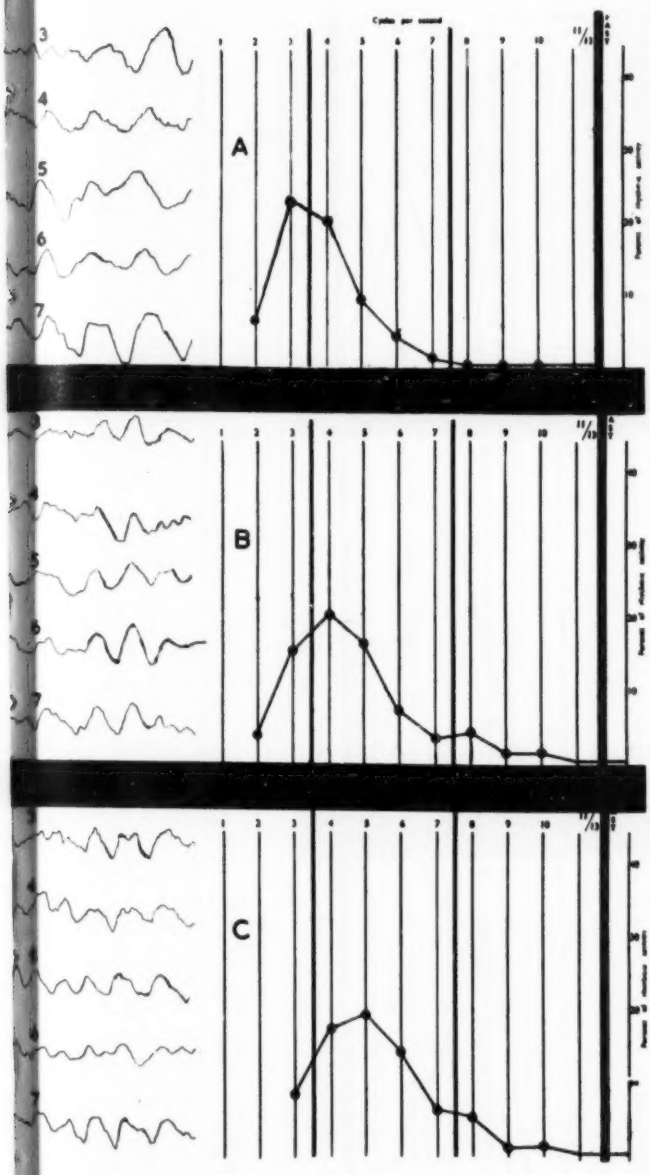

FIG. 5.—Case 1. See text.

(3) There is less rhythmic activity after recovery than in the earlier records. In *E* and *F* rhythmic activity averages 57% of the epoch, in *A* to *D* inclusive the average is 79%.

(4) There is a broader frequency spread in the transition phase records (*B*, *C*, and *D*).

Fig. 7 (Case 2) shows three records from a normal young male subject weighing 12 st. before (*A*) and 10 minutes (*B*) and 27 minutes (*C*) after the rapid ingestion of 75 ml. of absolute alcohol diluted five times with lemon-flavoured water. The following points of interest are seen: (1) All the records lie within the normal range and show normal frequency patterns with sharp peaks in the alpha band. (2) After alcohol there is a progressive shift of the frequency pattern as a whole towards slower frequencies and of the dominant frequency from 10 to 9 to 8 c./sec. This shift is demonstrated clearly in the patterns whereas it is less easy to see in the original records. (3) There is appreciably more rhythmic activity after alcohol.

In order to give some measure of the accuracy of assessment and of the significance to be attached to the shift in frequency pattern shown in Fig. 7, frequency counts from the same subject for six 50-second epochs are given in Table I and charted as frequency patterns in Fig. 8. There are two patterns from consecutive epochs immediately before alcohol was given and one

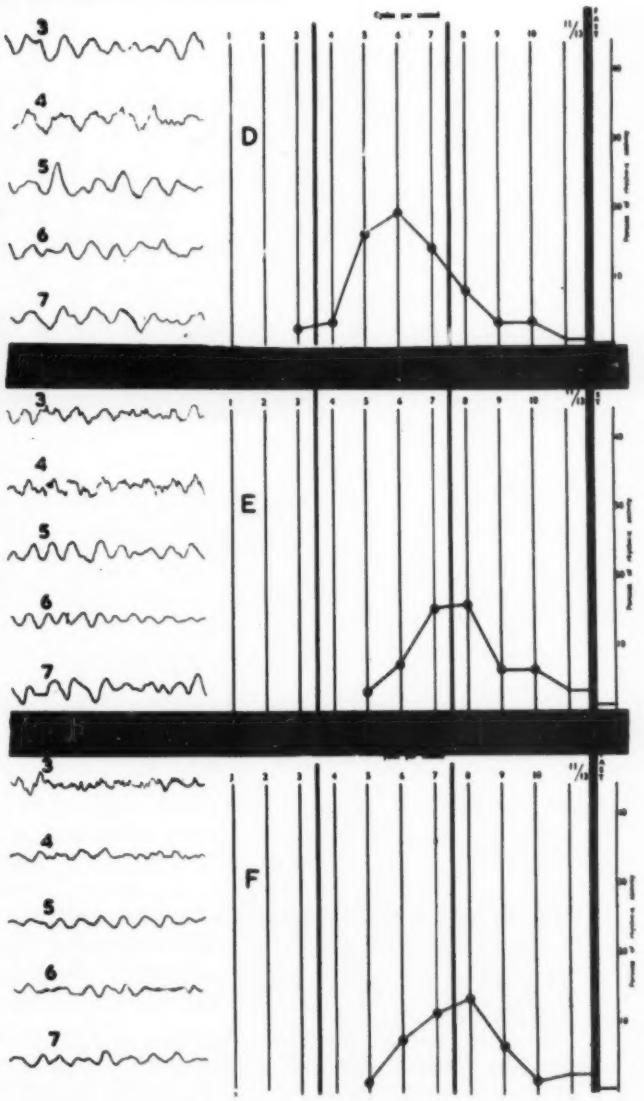

FIG. 6.—Case 1 contd. See text.

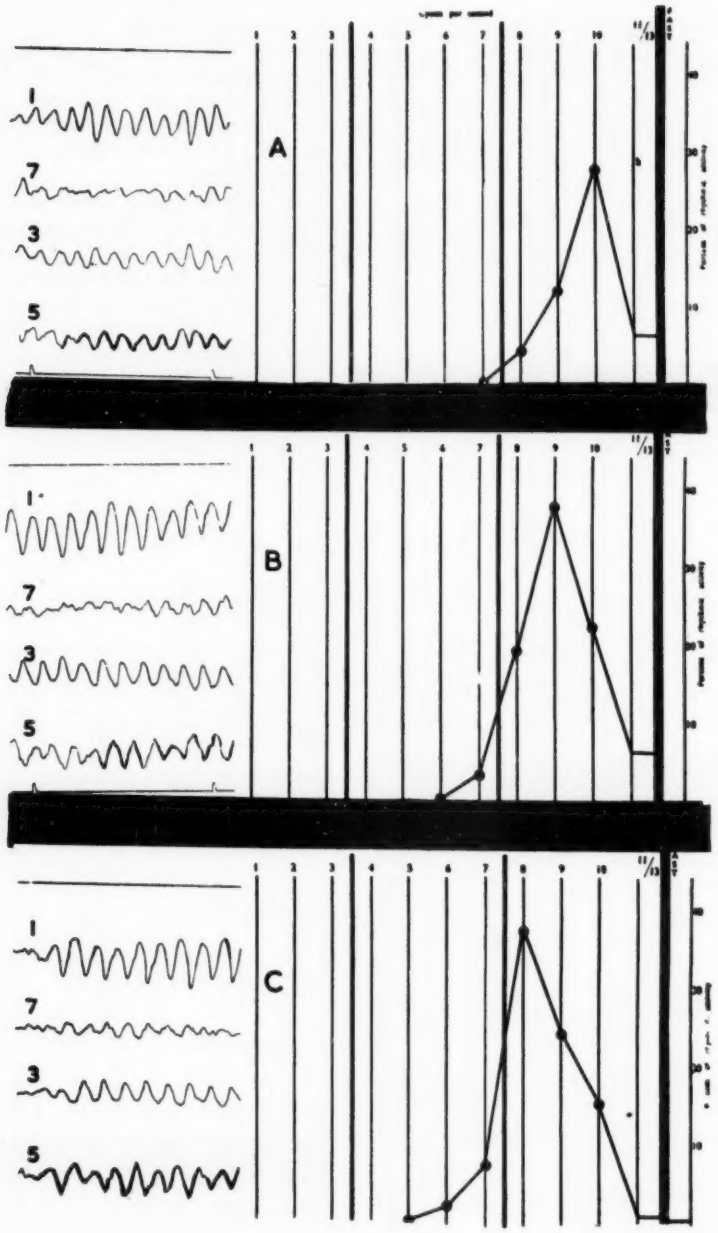

FIG. 7.—Case 2. See text.

from the same subject three weeks later (continuous line in Fig. 8) and three counts from epochs recorded 27, 29, and 41 minutes after ingestion of alcohol (broken line in Fig. 8) at which times the maximum E.E.G. effect of alcohol was obtained.

It will be seen that the patterns fall into two groups: the three control patterns uninfluenced by alcohol, group A corresponding to *A* in Fig. 7, and three patterns after alcohol, group C, corresponding to *C* in Fig. 7. Each pattern in group A has a similar shape and dominant frequency at 10 c./sec.; they differ from each other in the area under the curve, a measure of the amount of rhythmic activity in the epoch, which is probably a function of the subject's state of attention. The group C patterns differ from each other very little and they each have a dominant frequency at 8 c./sec. It can be seen quite clearly that the inter-group difference is much greater than the intra-group one.

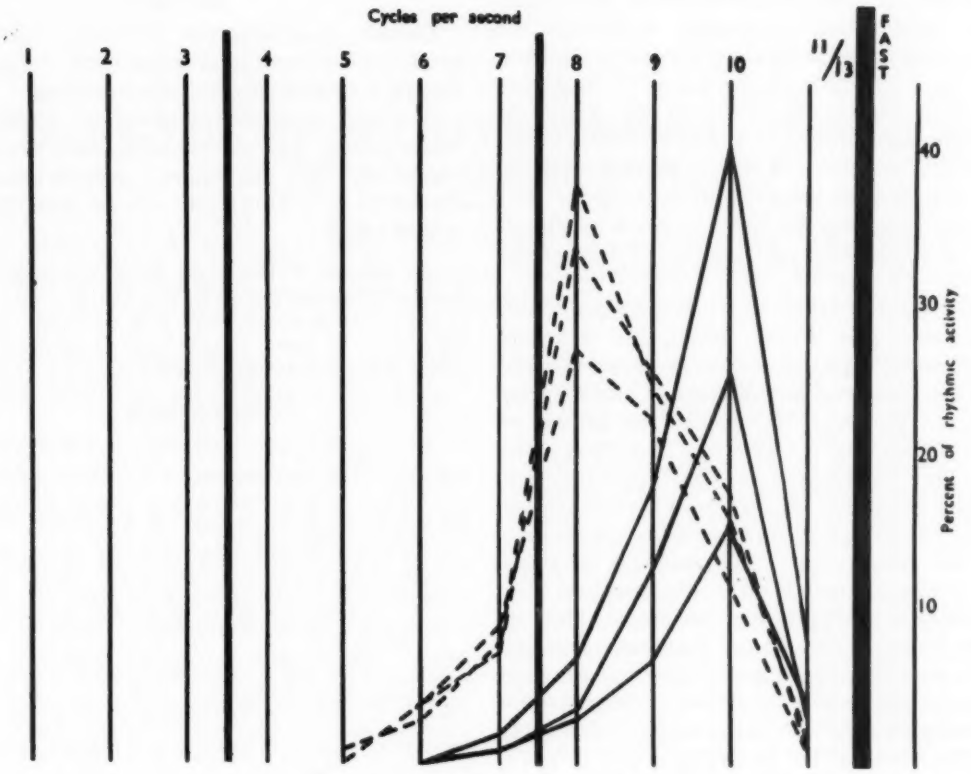

FIG. 8.—Case 2. Frequency patterns before alcohol (continuous line) and after alcohol (broken line). See text and Table I.

TABLE I

FREQUENCY COUNTS EXPRESSED AS PERCENTAGES OF TOTAL TIME OF SIX 50-SEC. EPOCHS IN SAME SUBJECT BEFORE AND AT VARIOUS TIMES AFTER INGESTION OF ALCOHOL

	Group	Percentage of Total Time of Rhythmic Activity at Different Frequencies						
		5	6	7	8	9	10	11/13
Before alcohol 1	A	0	0	2	7	18·5	40·5	8
Before alcohol 2	A	0	0	1	3	7	16	4
Three weeks later	A	0	0	1	4	13	26	3
27 min. after alcohol	C	0	4	9	27·5	23	12	1
29 min. after alcohol	C	1	3	8	38	25	16·5	1·5
41 min. after alcohol	C	0	4	7·5	34	26	18	1

Discussion

Simple inspection of records shows clearly that in certain disorders, which do not primarily affect the brain, the E.E.G. can provide evidence of cerebral dysfunction. Further, if serial records are taken, changes in the E.E.G. abnormalities may be seen which give a measure of variation in the severity of this dysfunction, a measure which, because it is often more sensitive than physical or psychological examination, has considerable clinical value. The method which has been described for expressing a generalized E.E.G. abnormality as a frequency pattern was developed in order to improve on assessment by inspection and to provide a graphic form in which this assessment could be passed on to the clinician in charge of the patient.

The conversion of complex wave forms to percentages should not be allowed to suggest a spurious accuracy. The frequency patterns have no intrinsic theoretical significance: they have been derived empirically. They have proved useful in demonstrating the extent of manifest changes and in showing slight variations which were difficult to detect in the original records. Their simple graphic

forms are easy to compare and contrast and studies of these forms may emphasize variations not readily obvious in the more complex primary record. Starting as a method of representing frequency changes with known alterations in the degree of delirium, the use of frequency patterns has already suggested that variations in the amount of rhythmic activity, spontaneous intra-record fluctuations, and the extent of frequency changes produced by stimuli may be of importance and worthy of further investigation.

The limitations of visual methods are fully appreciated (Dawson and Walter, 1944), and it is not suggested that a frequency pattern so derived should represent the precise electrical changes which occur in the brain. However, the method has proved of practical value (Read, Haslam, Laidlaw, and Sherlock, 1958; Sherlock *et al.*, 1958) and, although it takes time, it requires nò complicated or expensive equipment. Preliminary work with visually derived patterns has shown that the assessment of small changes in generalized E.E.G. abnormalities has sufficient clinical and probably theoretical value to justify the development of an automatic method which will save time, increase accuracy, and, it is hoped, reveal new facts of importance. The present method has been described because it will form the basis for any new method and because it may be of interest to those concerned in the development of electro-encephalography as a tool in the investigation of general medical disorders.

Summary

Certain disorders, not primarily cerebral, may produce alterations in consciousness and generalized electro-encephalographic abnormalities.

A simple empirical method of assessing these abnormalities and representing them graphically is described. Two illustrative examples are given and the scope and limitations of the method are discussed briefly.

I would like to thank the Medical Research Council from whom I receive a personal grant, Dr. Sheila Sherlock under whose care were most of the patients investigated, Miss A. M. Lees, electroencephalographer, and Dr. Denis Hill for his help and advice.

References

Adams, R. D., and Foley, J. M. (1953). *Res. Publ. Ass. nerv. ment. Dis.*, **32**, 198.
Brazier, M. A. B., and Finesinger, J. E. (1944). *J. clin. Invest.*, **23**, 303.
Clark, E. C., and Bailey, A. A. (1956). *J. Amer. med. Ass.*, **160**, 455.
Conn, H. O., Dunn, J. P., Newman, H. A., and Belkin, G. A. (1957). *Amer. J. Med.*, **22**, 524.
Dawson, G. D., and Walter, W. G. (1944). *J. Neurol. Neurosurg. Psychiat.*, **7**, 119.
Engel, G. L., Romano, J., Ferris, E. B., Webb, J. P., and Stevens, C. D. (1944). *Arch. Neurol. Psychiat. (Chicago)*, **51**, 134.
Holmberg, G., and Martens, S. (1955). *Quart. J. Stud. Alcohol*, **16**, 411.
Holmes, J. McD. (1956). *Brit. med. J.*, **2**, 1394.
Leinwand, I., Duryee, A. W., and Richter, M. N. (1954). *Ann. intern. Med.*, **41**, 1003.
Read, A. E., Haslam, R. M., Laidlaw, J., and Sherlock, S. (1958). *Brit. med. J.*, **1**, 963.
Sherlock, S., Read, A. E., Laidlaw, J., and Haslam, R. (1958). *Ann. N.Y. Acad. Sci.*, **71**, 430.
Summerskill, W. H. J., Davidson, E. A., Sherlock, S., and Steiner, R. E. (1956). *Quart. J. Med.*, **25**, 245.
Walton, J. N., Kiloh, L. G., Osselton, J. W., and Farrall, J. (1954). *Electroenceph. clin. Neurophysiol.*, **6**, 45.
Westlake, E. K., and Kaye, M. (1954). *Brit. med. J.*, **1**, 302.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 77.

PROCEEDINGS OF THE SOCIETY OF BRITISH NEUROLOGICAL SURGEONS: 58th MEETING

The 58th Meeting of the Society of British Neurological Surgeons was held at the Walton Hospital, Liverpool, on December 5 and 6, 1958. The President, G. S. Clark-Maxwell (Derby), was in the Chair. Dr. J. Poppen (Boston, Mass.) attended as the special guest of the Society.

Two Unusual Cases: Multiple Meningiomata Preceded by a Spinal Neurofibroma and "Spontaneous" Atlanto-axial Dislocation

Mr. A. SUTCLIFFE KERR (Liverpool) reported a case of a single woman aged 50 from whom a neurofibroma had been removed from a spinal nerve root in 1937 by Sir Geoffrey Jefferson. In 1955 she had a right-sided sensory Jacksonian epileptic attack and in 1956 investigations for further similar attacks suggested a lesion alongside the falx cerebri although the ventriculogram was difficult to interpret. A left frontoparietal craniotomy revealed two small parasagittal meningiomata and two near the Sylvian point, one being 4 cm. in diameter. These were removed but no attempt was made to reach the lesion of the falx nor to remove another tumour which could be felt in the region of the lesser wing of the sphenoid.

The epilepsy continued at three-weekly intervals although without loss of consciousness, but in 1958 she was found to have a right homonymous hemianopia, astereognosis of the right hand, a right spastic hemiparesis, and paralysis and wasting of the left side of the tongue.

X-ray therapy was given, a total of about 4,200 r. being spread over the whole calvarium. It caused considerable general and neurological upset but there had been steady improvement for two months. She could now walk with support although she still had minor epilepsy and an almost complete right hemiplegia with the other neurological signs unaltered. Her vestibular reactions were normal and she was not deaf. She showed no evidence of von Recklinghausen's disease nor was there any family history of that condition.

The second case was that of a boy, born in 1940, who suffered from rheumatic fever with carditis at the age of 6. When he was 10 years old he had some unsteadiness of the legs and a dislocation of the first on the second cervical vertebra was discovered. This was said to have been reduced and a leather collar was fitted. The boy had a further attack of rheumatic fever in 1951 and further manipulations of the neck were undertaken.

In 1953 he had increasing neurological disabilities and was treated by further manipulation, head traction, and, later, a Minerva jacket. Despite this his right arm became almost completely paralysed and all the other limbs were weak and spastic. When an occipital pressure sore had healed, skull traction was applied and parallel rib grafts were inserted between the occiput and the second, third, and fourth cervical spines after removal of the whole of the posterior arch of the atlas.

Following a severe temporary deterioration of his neurological condition he made a remarkable recovery and he resumed normal schooling two years after the operation. Unfortunately he developed cardiac failure and bacterial endocarditis and died three and a half years after the operation.

Aneurysms of the Middle Cerebral Artery

CAMPBELL CONNOLLY (Birmingham) discussed the changes which might occur following interruption of the middle cerebral artery or its branches in the surgical treatment of an aneurysm. Other workers had shown that large communications existed between the anterior and middle cerebral arteries and that there were smaller communications between the posterior and middle cerebral arteries. Angiograms were shown demonstrating such anastomoses. Previous writers had also noted that after occlusion of the middle cerebral arteries in dogs and monkeys there was no neurological abnormality after 24 hours provided the blood pressure was kept at normal levels. When hypotension was produced by bleeding there was severe neurological disturbance (Thompson and Smith, 1951).

Seven patients were described. In one there was an aneurysm of the middle cerebral artery on the non-dominant side with an intracerebral haematoma. The haematoma was evacuated and the aneurysm excised, the main stem of the middle cerebral artery being divided 3 cm. from its origin. Three months after operation the only neurological disability was a left homonymous hemianopia.

In six other cases main branches of the middle cerebral artery were interrupted during obliteration or excision of an aneurysm. In five of these, the aneurysm was on the dominant side and four of these had intracerebral haematomas. One patient, who had an intracerebral haematoma and was operated on *in extremis*, died. One was dysphasic and hemiparetic after operation but improved steadily. The remaining four suffered no increase in the pre-operative disability and improved steadily.

It was considered that temporary clamping of the main stem of the middle cerebral artery proximal to an aneurysm was dangerous as, should bleeding occur, it would consist

entirely of blood supplied from collateral arteries so that the part of the brain supplied by the middle cerebral artery distal to the clamp would be virtually exsanguinated. Severe brain damage might, therefore, be caused in a very short period of time.

It was concluded that in attacking aneurysms of the middle cerebral artery directly efforts should be made to preserve the vessel and all its branches, but, should it be necessary to sacrifice a branch, there was a good chance that no serious neurological disability would result.

REFERENCE

Thompson, R. K., and Smith, G. W. (1951). *Trans. Amer. neurol. Ass.*, 76, 203.

Intracranial Haemorrhage in Childhood

C. B. SEDZIMIR (Liverpool) presented a review of intracranial haemorrhage occurring in children under 16 in a five-year period 1954-58. The material was drawn from neurosurgical, cardio-paediatric, and general paediatric services in the Liverpool area. During this period 26 children were found to have had intracranial haemorrhages. The causative diseases did not differ materially from those found in adult patients, Aneurysm was the commonest cause and was present in 11 patients, all but one over the age of 10. The site of the aneurysm had much the same distribution as in adults. Five patients had arteriovenous anomalies, the youngest patient being under 2 years of age. In one patient an intracerebral haematoma and in five others subarachnoid haemorrhage occurred without investigation disclosing any aetiological factor. In all these patients multiple carotid and vertebral angiograms were done in an attempt to find a cause. In three patients intracranial bleeding was associated with blood dyscrasia, leukaemia in two, and purpura in one. In two patients the intracranial bleeding was associated with coarctation of the aorta; in one of them both lesions were treated surgically with good results.

Brain Changes in Fatal, Ruptured, Intracranial Aneurysm

B. E. TOMLINSON (Newcastle) described the brain changes in 32 fatal cases of ruptured intracranial aneurysm. At necropsy, the brain was only examined externally and the ruptured aneurysm identified where this was possible without disturbance of blood within fissures or sulci. After fixation, the vessels were dissected off and examined and large slices of brain made to study the distribution of the blood; multiple histological sections were examined.

Multiple vascular lesions were found in 15 instances (46%); in 14 multiple aneurysms were present, and in one, an angioma in addition to an aneurysm. The site of the aneurysms was similar to those reported in other series. Two small subdural haematomas were seen.

Surface subarachnoid bleeding was sometimes scanty when large collections of blood (subarachnoid haematomata) were present between the frontal lobes, in the Sylvian fissures, or in the depths of sulci. Nine very large collections of blood, partially, or entirely confined to the subarachnoid space, were seen (28%). Three were in the Sylvian fissure, from middle cerebral aneurysm rupture; two had caused limited intracerebral bleeding by breaching cerebral tissue at a distance from the aneurysm, one by opening up the deep limits of a sulcus on the insular cortex. Six subarachnoid haematomata resulted from rupture of anterior cerebral or anterior communicating aneurysms. In four of these the blood lay largely between the frontal lobes; in one it lay over the infarcted corpus callosum and in one it had burrowed extensively into the olfactory sulcus. In five of these instances massive infarctions were present. Several other instances of smaller localized collections of blood were seen.

Intraventricular and intracerebral haemorrhage in quantity was seen 17 times. It was considered that most resulted from localized collections of subarachnoid blood extending into sulci, or stretching brain tissue, until they extended into the brain. In only six was the aneurysm adherent to the brain.

Ischaemic lesions were found in 25 cases (78%) and in 13 (40%) they involved the whole, or a large portion, of a major artery territory. The lesions were usually, but not always, in the distribution of the artery on which the ruptured aneurysm occurred. Four massive infarctions involved the anterior cerebral artery territory, on three occasions bilaterally. In eight cases, the infarcted area was of middle cerebral artery distribution; in two the posterior cerebral artery supply was also involved.

One instance of infarction of posterior cerebral artery distribution alone was seen.

In 10 of the 13 instances of major infarction, subarachnoid or intracranial haematomata were present.

It was thought that localized collections of blood in sulci or fissures were of importance in several ways: by acting as space-occupying lesions; by stretching cerebral tissues until intracerebral or intraventricular haemorrhage occurred; and probably by inducing infarction. The possible mechanisms by which localized collections might produce ischaemic lesions were stretching or kinking of vessels by the haematoma; tearing of small branches passing from major vessels to the brain; and spasm induced by stretching. Simple drainage of the bleeding site might prevent some of the fatal complications.

An additional unexplained finding was granular cell degeneration of the cerebellum in four instances. In view of the absence of clinical evidence of cerebellar dysfunction in these cases and the absence of histological reaction to the degeneration, this was considered a terminal phenomenon.

Mental Abnormalities following Subdural Haematoma

F. L. DAVIES (Haywards Heath) discussed the incidence and treatment of mental disorders in patients with subdural haematoma. In a recent series of 44 consecutive head injuries admitted to a neurosurgical unit 11 had subdural haematomas. These patients were selected for admission from a much larger number of head injuries occurring in the area. Of the 11 cases, four were cured and discharged home. Four were transferred to a mental hospital with various types of mental disorder. Two of these died in the mental hospital and the other two remained in hospital a year after injury. Three patients

died at some time after operation, thus making a total mortality of 45.4%. The considerable incidence of subdural haematoma in the group was thought to be related to the high average age of a population of retired persons in coastal resorts, and in the subdural group 10 of the 11 patients were over 50 years of age. The high mortality rate was also thought to be related to high age groups in which patients were unable to combat respiratory infections. Immobility in bed, often occasioned by mental disorder, may have been a contributing factor.

Previous workers had reported a low incidence of mental disorders after head injuries. Predisposing factors considered were sex (in this series all patients with mental disorders were males), arteriosclerosis, and alcohol addiction.

In the present series confusion was present in seven cases and remained a permanent feature in four. Personality disorder was found in one case and dementia in three, one complicated by aggressive hallucinations. Korsakov psychosis was found in one case.

In all cases mental abnormalities began after a unilateral or bilateral subdural haematoma or hygroma had been treated surgically. In four patients the brain did not expand after removal of the haematoma and this feature appeared to have serious significance, as three of these died, the fourth making a good recovery. The interval between injury and operation did not appear to affect the final results; one patient with the longest time interval before operation made a satisfactory recovery and another patient operated on the day after injury died four days later. It was suggested that vascular thrombosis superimposed on arteriosclerosis was responsible for the failure of the brain to expand.

The importance of adequate surgical treatment was stressed, including attempts to expand the brain by saline injections. The importance of general care was also stressed especially control of respiratory infection and adequate dietary intake. Mental treatment consisted of psychotherapy, occupational therapy, and mental and physical rehabilitation.

The Temporal Approach to Tumours of the Sella Turcica in the Presence of a Prefixed Chiasma

JAMES L. POPPEN (Boston, Mass.) discussed the temporal approach to tumours of the sella turcica in the presence of a pre-fixed chiasma. He noted that for many years tumours of the sella turcica had been attacked surgically either by the frontal or transphenoidal routes (Hirsch, 1910; Jefferson, 1940), the exception being the temporal approach used routinely by Horsley in a series of 14 patients. Jefferson (1957), in the Centenary Lecture, believed that it was natural for Horsley to use this approach since his research studies on the pituitary body had been carried out mainly in the dog and monkey. The natural and easiest route in these animals was the temporal. Neurosurgeons had approached the large extrasellar extensions under a temporal lobe as one would approach a temporal lobe tumour.

The surgical management of only the tumours that involve the pituitary body, the posterior clinoids, the upper half of the clivus, and the sphenoid sinus were discussed. These lesions were limited anteriorly by the chiasm of the optic nerve, posteriorly by the pons, and superiorly by the third ventricle.

Fortunately these tumours were relatively rare. Surgical attention had been required in only 12% of their cases of pituitary adenoma since the introduction of the rotational two million volt *x*-ray apparatus. Operation was carried out only for those adenomas that were cystic or haemorrhagic or when the vision was so precarious that immediate operation was advisable. There was also the rare individual who demanded surgery rather than the slower method of *x*-ray therapy. It was also possible that the surgeon, at times, became a bit anxious to demonstrate his prowess. This was especially true since removal of the hypophysis had been given a temporary impetus by many neurosurgeons for the treatment of cancer of the breast. That particular form of treatment would, of course, find its proper place in due time.

The tendency to enlargement of pituitary adenomas was by no means uniform. They most frequently extended through the diaphragma sellae upward if the anterior and posterior clinoids were sufficiently strong and, as the tumour enlarged, the tendency was to carry the chiasm upward, thus causing early visual changes. In other patients the posterior clinoids might be abnormally thin, allowing the adenoma to follow the line of least resistance posteriorly. In this way the tumour could become of significant size before vision was affected. Certainly in these patients the chiasm was most likely to be prefixed. In a sella turcica with a thin floor and a large sphenoid sinus the tumour extended inferiorly. This, perhaps, was the reason why visual changes developed late in the course of the disease in so many of the chromophile (acromegalic) patients, because of self-decompression of the adenoma into the large sphenoid sinus as well as the ethmoid sinus. In patients with suprasellar tumours or tumours of the upper portion of the clivus and posterior clinoids, pressure signs developed before visual changes became manifest, whereas in tumours of the tuberculum sellae visual changes always developed before increased intracranial pressure occurred.

If it had been decided that surgery was mandatory, air studies and arteriograms were of particular aid in determining the approach most likely to give the best results. If the anterior cerebral arteries were displaced posteriorly and upward with only slight opening of the carotid siphon, the anterior or frontal approach was the procedure of choice. If the posterior clinoid was eroded and the anterior clinoid reasonably normal, with little or no undercutting of the tuberculum sellae, and the angiograms showed considerable opening of the carotid siphons the temporal approach was more likely to give a better exposure of the tumour. If no obstructive signs were present, he had found that encephalograms seemed to give the more accurate and definite location of the tumour and, incidentally, the approximate location of the optic chiasm. The tumours that were favourable to this approach, therefore, included craniopharyngiomas, adenomas, chordomas, meningiomas of the upper portion of the clivus and dorsum sellae, epidermoids, and the large pituitary adenomas with a prefixed chiasm.

Following air and angiographic studies, if the tumour was thought to be in the location described, adequate pre-operative preparation, which included steroids and intravenous urea solution, was given. The patient was placed in the sitting position (tic position) and the incision outlined. The anterior limb of the incision only was opened initially. An opening was made in the inferior portion of the squamous part of the temporal bone. The dura was opened with the loose flap turned down, then sewn to the soft tissues inferiorly. A ventricular puncture of the temporal horn was made if the brain was tense. Usually the intravenous injection of urea caused the brain to shed much of its fluid content, allowing the temporal lobe to be readily elevated for sufficient exposure of the tumour. If not, the anterior-inferior portion of the temporal lobe might be sacrificed. It had been of considerable surprise to him to find that tumours which had eroded the sella turcica and destroyed the posterior clinoid were much more superficial than would be supposed, contrary to the impression received when an attempt was made to clip a vestigial aneurysm of the internal carotid artery that extended posteriorly along the course of the posterior communicating and anterior choroidal arteries. The distance from the temporal bone seemed to be much greater. This was due, no doubt, to the contour of the temporal fossa and depended on whether it was shallow or deep.

Since the width of the temporal fossa from the inferior edge of the squamous temporal bone was only 5 to 6 cm., it could be readily seen that if the sella was ballooned out and the posterior clinoids eroded, tumours, even though extending only a slight distance laterally, made the approach relatively shallow and simple. The more inferiorly the squamous portion of the temporal bone was removed, the easier the approach. Rarely was it necessary to extend the incision that had been outlined and the bone flap turned down. If perchance the frontal approach was used initially with the impression that the chiasm was not prefixed, but on direct examination it was found to be prefixed, the inferior limb of the frontal incision might be lengthened to the upper border of the zygomatic bone and the temporal approach used. This avoided subjecting patients to an added procedure at a later date. It was also of help if bleeding that could not be properly controlled had been encountered in the tumour during the anterior approach. This was particularly true of the vessels that might be separated from the circle of Willis in a blind attempt to remove the capsule of the tumour when the anterior approach was used.

Four craniopharyngiomas had been attacked in this manner. One patient died of post-operative thrombosis of the internal carotid artery which was markedly arteriosclerotic and had a saccular aneurysm attached. No necropsy was allowed. Four adenomas were managed in this fashion; two of the patients died. Five chordomas were extensively removed with no operative deaths; and one meningioma of the clivus was also removed.

In the use of this approach it should always be remembered that since the tumour could be visualized so readily, one was inclined to excise more radically than was necessary, as was the case in the two pituitary adenomas. All of the capsule that was not adherent to major vessels could be readily removed. The capsule that was firmly adherent to the artery should be allowed to remain intact, however, and *x*-ray treatment given subsequently. The cystic tumours presented no particular problem since the capsule peeled away readily. The third nerve must be protected, especially during coagulation of any bleeding points or during manipulation of the tumour.

It was suggested that the temporal approach be used in patients in whom the tumour extended into the third ventricle or compressed the anterior-superior portion of the pons and in pituitary tumours with a prefixed chiasm.

References

Hirsch, O. (1910). *J. Amer. med. Ass.*, **55**, 772.
Jefferson, G. (1940). *Proc. roy. Soc. Med.*, **33**, 433.
—— (1957). *Brit. med. J.*, **1**, 903.

On Certain Acute Head Injuries

Doreen Jacobs (Liverpool) described five cases of acute head injury all posing diagnostic problems with regard to either the anatomy or pathology of the condition.

Case 1.—A man, aged 54, with a known right-sided injury, developed rapidly a left hemiplegia associated with a dilating pupil on the left. An acute subdural haematoma was found in the left temporal region. He had thus sustained a contre-coup haematoma associated with an ipsilateral hemiparesis. It was concluded that, irrespective of conflicting physical signs, the side of a dilating pupil indicated the site of pathology.

Case 2.—A man, aged 20, during a five-hour period of observation after an accident, developed a dilated left pupil. Carotid angiography disclosed a right temporal haematoma. The dilated pupil proved, later, to be part of an ophthalmoplegia presumed to be due to direct trauma to the nerves despite its delayed onset. This case appeared to invalidate the conclusion drawn from Case 1.

Case 3.—A man sustained a head injury and was found to have unequal pupils. Examination disclosed that he had one glass eye.

Case 4.—A child, aged 5 years, sustained a relatively minor head injury and over a period of two weeks developed papilloedema and a sixth nerve paresis. She proved to have a small depressed fracture obstructing the posterior end of the sagittal sinus which had not been radiologically obvious. Angiography suggested a sagittal sinus block. Exploration confirmed the diagnosis and relieved the condition.

Case 5.—A child, aged 9 years, presented with a calcified extradural haematoma three months after a head injury. The only physical manifestation of intracranial pathology was the development of epilepsia partialis continua seven weeks after the accident. This was controlled by medication and did not recur. The diagnosis of a space-occupying lesion was made by angiography and the exact pathology found and relieved by exploratory craniotomy.

It was concluded that these cases served to emphasize that patients were individuals, with individual good or bad fortune, individual physical signs, and a bias against any dogmatic classification.

A Review of 700 Cases of Epilepsy

R. H. HANNAH (Liverpool) reviewed 700 cases of epilepsy. These cases had presented themselves for investigation at a neurosurgical unit over a period of 11 years. Four hundred and fifty-eight of the cases were male and 241 female. Six hundred and twenty-nine were alive, 57 dead, and 14 presumed dead. An up-to-date follow-up was available in 435 cases. The series showed a reasonable representation of all age groups. Pneumo-encephalographic studies were available in 616 cases and E.E.G. reports in 463. A family history of epilepsy was obtained in 13·1% of a sample of 595 cases.

The cases were classified on an aetiological basis and on clinical findings. On the former basis the series was broadly divided into cases showing structural changes in the brain, as shown by air studies, and those with normal pneumo-encephalograms. Those showing organic changes were subdivided into (1) those associated with space-occupying lesions (68); (2) those having birth injuries or head injuries (122); (3) those with a focal cicatrix in the brain (8); (4) those showing diffuse organic changes (153), 84 of these attributable to a variety of infections or degenerative conditions and 69 were of uncertain aetiology; (5) those associated with cerebrovascular disease (49); (6) those with congenital anomalies (20).

Those cases with no demonstrable organic change were subdivided into (1) those with generalized attacks or petit mal (174), (2) those with focal attacks (102); (3) those associated with generalized metabolic changes (4).

On clinical grounds the cases were divided into generalized, petit mal, focal motor, focal sensory, and focal psychical. There were 373 cases with generalized and 327 attacks with focal epilepsy.

The ages of onset of the seizures were considered. The highest incidence of epilepsy due to birth injury was in the first decade; due to supposed centrencephalic causes in the second decade; due to head injuries in the third decade; due to space-occupying lesions in the fifth decade; and due to cerebrovascular disease in the sixth decade.

By comparing the duration of the epilepsy in cases with and without demonstrable organic brain changes it was shown that the duration had little relationship to the degree of brain atrophy. It was suggested that the brain changes might be the cause of the epilepsy rather than the result of it.

Of the 463 cases with E.E.G. reports available, 367 were abnormal. The generalized electrical activity corresponded to generalized seizures in 81·2% of cases and focal activity to clinically focal attacks in 70·3 %.

In 304 cases information regarding birth was available. Of this sample, 30·2% showed evidence of abnormality of birth. In 402 cases information was available regarding birth injuries. Fifty-three cases had a history of injury at birth but only 31 showed abnormal air studies. Seventy-seven per cent, or 449 cases, had a history of infantile convulsions.

The association of epilepsy with menstruation was investigated. Ninety-three women supplied information and there was an association in 38 cases. The majority of these fell into the groups of attacks of supposed centrencephalic origin.

Some Unusual Cases of Neurosyphilis

ROBERT HUGHES (Liverpool) described a series of unusual cases of neurosyphilis seen in Liverpool during the past few years.

Case 1.—A woman, 53 years, had a one-year history indicating a dementia paralytica. When first seen the pupils were normal; a fortnight after admission to hospital she developed typical Argyle-Robertson pupils. A month after chemotherapy had been begun the pupils became almost normal although the left was slightly sluggish in reaction to light and accommodation. Her mental symptoms disappeared but at a later date she had some epileptic attacks.

Case 2.—A woman, 61 years, was diagnosed as having tabes dorsalis in 1941 and had a course of 12 injections. For a period of 15 years her neurological state deteriorated, until when seen in 1946 she was unable to stand without assistance. She had gastric crises and loss of sensation in the legs below the knees. She had been seen at various hospitals throughout this period and her serological reactions were completely negative. Unfortunately no treatment had been given and when at last effective chemotherapy was started in 1956 there was no improvement.

Case 3.—A man, 29 years, had a history of one attack of unconsciousness two years before, and was seen at an out-patient clinic with early papilloedema, and a brain tumour was suspected. The eye trouble disappeared completely on anti-syphilitic treatment.

Case 4.—A man, 49 years, had shown marked mental deterioration for the past year, some evidence of a right frontal lobe lesion clinically, and an E.E.G. showed a delta focus in this area. A brain tumour was suspected but on serological reactions this was thought to be a case of dementia paralytica.

Case 5.—A woman, 21 years, described attacks of blurring of vision of the left eye and double vision during the past year, and more recently weakness of the right side of the body. Disseminated sclerosis was suspected but the condition proved to be syphilitic.

Case 6.—A man, 40 years, was admitted as an emergency in June, 1958, with an acute lesion in the right cerebral hemisphere, neck rigidity, temperature 102°, and large numbers of polymorphs in the cerebrospinal fluid. The E.E.G. showed a delta focus in the right hemisphere. A brain abscess was suspected but the condition proved syphilitic and responded rapidly to chemotherapy.

Case 7.—A woman, 64 years, had had cerebellar ataxia of one year's duration. At first this was thought to be a carcinomatous neuropathy as she had had an adeno-carcinoma of the colon removed five years previously. The condition proved syphilitic and during the following two years there was no evidence of a recurrence of the carcinoma.

Cases 8 to 10 were instances of neurosyphilis precipitated by head injury.

He stressed that neurosyphilis was still frequently seen in his clinic and should be considered in all neurological cases.

The Anatomy of Thalamic Pain

D. BOWSHER (Liverpool) presented the results of some investigations on the brain-stems of patients dying at suitable intervals after antero-lateral cordotomy, using the Nauta silver technique. These results had confirmed

and extended the observations of previous authors on the widespread connexions of fibres from Gower's tract. Although a few fibres passed directly to the thalamus, there was a very large spino-reticular contingent ending chiefly in four zones of the ventro-medial reticular formation. Other fibres passed to the corpora quadrigemina, the inferior olive and lateral reticular nucleus, and to the sensory cranial nerve nuclei.

In one case dying 32 days after operation, preliminary and only very approximate fibre counts had been made in transverse sections stained by the method of Häggqvist. These counts suggested that, of the fibres present in Gower's tract at C.1 level of the cord, only 45% of small fibres (2-4μ) and 70% of large (4-7μ) reached the rostral medulla. At mesencephalic level only 12% of small and 36% of large fibres remained. These figures served to emphasize the quantitative importance of the spino-reticular element in Gower's tract.

It had already been suggested (Bowsher, 1957) that while direct spino-thalamic fibres were responsible for acute localized pain, the spino-reticular fibres were a link in a neuron chain by which diffuse, poorly localized pain or discomfort was eventually brought into consciousness. This second pain pathway bore a remarkable resemblance to the "reticular activating system", and this parallel was investigated electroencephalographically in patients with spontaneous "thalamic" pain accompanied by anaesthesia to acute pricking pain. It was found that the alpha rhythm was only desynchronized in those cases in which it was possible to evoke the diffuse pain. It was suggested that massive cortical "activation" by non-specific impulses travelling up diffuse reticulo-thalamo-cortical pathways was responsible for the "thalamic" type of pain.

REFERENCE

Bowsher, D. (1957). *Brain*, **80**, 606.

Observations on the Injection of Xylocaine into the Frontal Lobes

P. M. O'FLANAGAN (Liverpool) described the results of injecting "xylocaine" into the frontal lobes as a test for determining the probable results of a leucotomy. He noted that Fulton (1951) had suggested that where the therapeutic effect of leucotomy was in doubt the area in question could be injected with local anaesthetic as a trial. In order to evaluate this procedure a pilot study had been undertaken over the past two years.

One per cent. plain "xylocaine" had been injected bilaterally into the lower medial frontal quadrant approximately 1 cm. superior to the orbital plate and just anterior to the frontal horn of the lateral ventricle. The amounts injected varied from 2 to 9 ml. The subjects consisted of 18 psychiatric patients, including psychotics, psychopaths, and neurotics.

Complex autonomic changes occurred in 84% of the cases immediately after the second injection. No lateralization was shown. These changes included alteration in blood pressure levels, often sudden and marked, also apnoea up to 15 minutes, and unilateral or bilateral mydriasis.

Recovery of consciousness was sometimes delayed up to four hours whilst drifts in blood pressure, pulse rate, and body temperature, changes in skin coloration, and coarse muscle fasciculations were delayed responses. Independence was shown in the immediate responses to each other.

One male patient of 62 died of a cerebellar haemorrhage (5% mortality). One patient developed a thrombosis at the head of the right caudate nucleus and another a transient coma with hemiplegia and hyperthermia four days after injection. Both patients recovered fully.

E.E.G. investigations showed the following changes. In those patients with a profound fall in blood pressure there were hypoxic rhythms. Runs of 6 c./sec. activity were seen during the recovery phase after the fall in blood pressure. Desynchronization and decrease in amplitude of the orbital rhythms were also seen.

Statistical examination disclosed that apnoea was an unfavourable factor ($\chi^2 = 0{\cdot}1$ level of significance). The other autonomic responses showed no statistical relationship to prognosis.

Forty-seven per cent. showed no psychiatric improvement. Seventeen per cent. manifested short and equivocal improvement. Forty-five per cent. showed a loss of physical and mental symptoms lasting seven to 84 days. Of the latter group all but one were subjected to leucotomy, and 84% showed marked improvement or recovery.

It was concluded that a definite and maintained loss of symptoms with no excessive increase in extraversion after local injection appeared to justify a leucotomy.

REFERENCE

Fulton, J. F. (1951). *The Frontal Lobes and Human Behaviour* [Sherrington Lecture, 1951]. University of Liverpool.

The Spitz-Holter Valve

G. H. MCNAB (London) described his experiences with the Spitz-Holter valve in the treatment of hydrocephalus and showed a film of the operative procedure. He noted that the valve was designed to provide a unidirectional flow of cerebrospinal fluid from the lateral ventricle to the superior vena cava at a set pressure of 50 mm. water. The success of the new valve was due to the use of specially purified silicone rubber. This material was non-wettable and adherent to itself so that the valves could open and shut at the set pressure without loss of resilience. The slit valve caps never came in contact with blood so that the cerebrospinal fluid was retained within its own boundaries. He reported that Lawrence, working at The Hospital for Sick Children, Great Ormond Street, had investigated a series of 182 cases of hydrocephalus not subjected to any form of operation. Of these 89 had died, nine remained progressive, three were untraced, but most importantly 81 appeared to have undergone spontaneous arrest. Of these arrested cases, 75% were educable with an I.Q. of over 50 and 57% had a normal I.Q. Many suffered additional physical handicaps but 33% of the group were free from physical disability. It followed, therefore, that operative methods of treatment must offer at least 46% arrest of hydrocephalus and more than 57%

nust be able to attend a school for normal children provided their physical handicap would permit this.

He had inserted 60 of these valves over a nine-month period, 49 (81%) were still working. The cause of block was aqueduct stenosis in 16%, basal cistern block in 53%, and Arnold-Chiari deformity in 31%. In 19 cases there was an associated myelomeningocele and consequent risk of infection. Hydrocephalus was well advanced when treatment was started and the average depth of cortex was 7 cm. It was noted that whilst 2 cm. had been suggested as the minimum depth of cortex associated with normal intelligence, he had had several cases with cortex of only 1·5 cm. and I.Q. of 85 to 100. The average head circumference was 19½ in. and it was noted that with circumferences above 22 in. the cortical depth was always below 2 cm.

Eleven deaths had occurred in the series. Five cases of Arnold-Chiari deformity died with infected clot formation in the superior vena cava and heart. Five cases of basal cistern block died, three due to septic clot formation and two from excessive loss of cerebrospinal fluid following removal of a polythene tube from spino-ureteric drainage and removal of a valve from one side to the other. One case of aqueduct stenosis died from haemorrhage and infection following ventricular taps in another hospital. In all these cases the valve was found to be in working order at necropsy and the jugular catheter free of clot.

A full description of the valve was given and illustrated with the film. It was stressed that failure was due to clot forming on the wall of the vein at the end of the jugular catheter; minor trauma to the wall and excessive mobility of the tube might be causative factors. To prevent this, the tube was now secured at its entry to the internal jugular vein by the use of a nylon junction tube and the lumen of its distal portion had been reduced.

The Management of Malignant Cerebral Astrocytoma

PHILLIP HARRIS (Edinburgh) gave a preliminary report on the management of 62 patients with malignant cerebral astrocytoma seen during the period November, 1955, to November, 1957, when linear accelerator (4 MeV) radiotherapy had become available. The main advantages of supervoltage radiotherapy were less skin dose, no permanent epilation, a greater dose at depth and reduced bone absorption and therefore a higher tumour dose. It was found that whole head treatment was necessary to ensure that the whole of the tumour was being irradiated.

A decision regarding investigation and treatment was made partly on the clinical course; thus the prognosis was very poor (survival under three months) if there were severe neurological deficits and no treatment was attempted. The prognosis was better if raised intracranial pressure was the presenting symptom, and better still if the latter was epilepsy. By the age of 40 in men, and 50 in women, the prognosis was poor, over the age of 60 in either sex it was usually hopeless, below 35 years it was quite good.

Cerebral angiography was helpful in diagnosis, and also in prognosis. Thus 56 patients had this test. In 25 the typical tumour circulation of a malignant astrocytoma was seen, only two of these patients survived one year; of the 31 patients without a tumour circulation on angiography, nine survived one year and six others were well after a period of two years. A further three patients were well after one year and two after two years.

Kernohan's classification of astrocytomas was used (Svien, Mabon, Kernohan, and Adson, 1949). The majority of the tumours were in Grade 4. Nine without tumour circulation on angiography were in Grade 2; only one with circulation was in this grade.

Using the above criteria, 43 patients had surgical decompression (partial excision of tumour—usually by lobectomy, in 16); and 32 had a full course (4,500 r) of radiotherapy, with 50% survival of six months, and 30% of one year. This compared with 18% and 10% respectively in the 263 patients with a similar type of neoplasm seen in the previous five years.

Assessment of the results of treatment was based on the clinical state, and if available, angiographic and pathological changes. In three patients, a return of raised intracranial pressure one year after decompression and radiotherapy was due to cyst formation in the tumour site; there was a good response to further surgical treatment.

The present management of these most difficult and quite common neoplasms appeared to give improved results regarding the period of useful survival.

REFERENCE

Svien, H. J., Mabon, R. F., Kernohan, J. W., and Adson, A. W. (1949). *Proc. Mayo Clin.*, **24**, 54.

Some Experiences with Echo-Encephalography

ANTHONY JEFFERSON (Sheffield) presented his experiences with the Kelvin and Hughes Mark V flaw detector specially modified by the makers in collaboration with Dr. Douglas Gordon. Initially the frequency of the emitted ultrasound was 2·5 megacycles per second. More recently better results had been obtained with a frequency of 1·5 megacycles per second.

This apparatus might be of help in detecting the presence of, or in confirming the absence of, a supratentorial mass. He had not been able to demonstrate that it had any other diagnostic potentialities.

Fifty cases had been tested to date. In all of them there had been radiological or operative verification of the findings. In 31 cases with no midline displacement a central echo was satisfactorily obtained in 25 and with difficulty in three cases. In three cases the presence of displacement was falsely indicated. In 19 cases with midline displacement this was demonstrated satisfactorily in 13 and with difficulty in one. A central echo was falsely obtained in five cases. Some examples of the results were shown.

It was concluded that the flaw detector might give helpful information but it might mislead. It was easy to learn to use but sometimes its use was a little laborious. However, he agreed with Leksell (1956, 1958) that it provided a potentially valuable tool—possibly even more valuable after further slight modification. Already there had been occasions when the decision to transfer a patient to the neurosurgical department had been taken at the bedside from information derived from this device. He

noted that it would take time to establish the flaw detector in the diagnostic hierarchy and that the present report was in the nature of a preliminary communication designed to draw attention to the possibilities of the method. (He expressed his gratitude to Messrs. Kelvin and Hughes Ltd. who had generously loaned the apparatus.)

REFERENCE

Leksell, L. (1956). *Acta chir. scand.*, **110**, 301.
—— (1958). *Ibid.*, **115**, 255.

The Use of Paraspinal Acrylic Inlays in the Treatment of Cervical and Lumbar Spondylosis and Other Conditions

GEOFFREY KNIGHT (London) discussed the use of acrylic inlays in certain spinal conditions. He suggested that in degenerative and traumatic lesions of the spine referred pain from deep ligaments affected by altered mechanical stress was often more important than pain from root compression. Acutely painful or unstable joints could be supported and overstretching of ligaments prevented by placing an inlay under the paravertebral muscles on the posterior aspects of the laminae.

A sheet of acrylic plastic ("kallodent" preparation 222 range) was used for this purpose. If this was inserted in a soft, doughy consistency it would adapt to local curvatures and harden *in situ* within 24 hours. This slow setting was advantageous as the spine could be supported in the optimum position for 24 hours during which time the inlay adapted itself to the required position and formed a well-fitting and firm support. Correct consistency before insertion was important and this was usually obtained 20 minutes after the mixture of 3½ parts of acrylic polymer with 1 part of acrylic monomer. If the plastic was inserted while still tacky or moist an excess of serous fluid might form around the inlay. This reaction had occurred in certain cases in the lumbar region but never in the cervical. This might be due to the greater amount of material inserted but the risk of reaction was minimized by using a firm, dry inlay in a completely dry bed in which absolute haemostasis had been secured.

In the cervical region inlays had successfully relieved severe referred pain from areas of spondylosis and old, painful cases of fracture dislocation, thus enabling patients to discard collars which they had had to wear continuously. The operation was conducted in the sitting position, the inlay being inserted usually over the back of the fifth, sixth, and seventh laminae on one side only, after which the head was held in neutral position for 24 hours by a plaster back-slab.

A large inlay from the level of the occipital plate to the third cervical lamina had produced a satisfactory stabilization in a case of atlanto-occipital subluxation produced by rheumatoid arthritis.

In the lumbar region inlays had been employed in patients suffering from syndromes of low back pain with referred pain in the legs produced by overstretching of ligaments resulting from abnormal mobility of a lumbar vertebra. In these patients the spine was painless only in one balanced position. Pain was provoked by movement, by jarring of the spine while travelling, by walking, and by rotation of the spine when rolling over in bed. In the lumbar region, after the insertion of an inlay into a completely dry bed, the patient was nursed flat on the back with the spine slightly extended over a pillow for the first 12 hours and was allowed up at the end of three days.

Late Results in Five Cases of Communicating Hydrocephalus Treated by Theco-peritoneal Anastomosis

A. R. TAYLOR (Belfast) reported the results in five cases of children with communicating hydrocephalus treated by theco-peritoneal anastomosis, the survivors of eight so treated in 1952. These cases were studied by a psychologist, a psychiatrist, and a neurological surgeon. The parents had also been interviewed. They all fell into the I.Q. groups 100-110. None had gross personality disorders and all were progressing normally at school. The results had no relationship to the thickness of the surviving pallium before operation, which in one case was 0·5 cm. One child required a second operation in his third year; the others had presumably by then balanced their cerebrospinal fluid production-absorption mechanism as they had outgrown their tubes.

Ventriculo-Peritoneal Anastomosis in the Treatment of Hydrocephalus

J. M. ROBERTSON (Glasgow) presented his experiences in the treatment of infantile hydrocephalus by ventriculo-peritoneal anastomosis and discussed the value of this procedure in other neurosurgical conditions. This type of shunt was particularly useful in that it was applicable to both obstructive and communicating hydrocephalus. Much of the success of this operation was attributed to the silicone tubing used; this was elastic and pliable, did not kink or undergo any alteration in the tissues, and did not cause any tissue reaction.

The tubing, 1.5 mm. O.D., 0·5 mm. bore, was inserted into a lateral ventricle, usually the right, through a posterior parietal burr hole and fixed by a flanged silicone tube threaded over it and secured to the pericranium. Most obstructions in the tube were found at the distal end and all occurred within the first two months. Usually some debris was found lodged in the tube but in others no obstruction was found and usually re-positioning of the distal end of the tube in the peritoneum produced a satisfactory result. In a few cases washing through the tube with Fisher's solution by needling the tube through the skin had cleared the obstruction; in others exposure of the abdominal end of the tube had been necessary. Sepsis had been the sole cause of failure to establish drainage in the unsuccessful cases. In three of such cases the hydrocephalus was associated with a meningocele. The shunt was established first to drain the hydrocephalus and relieve tension in the meningocele. In each case infection supervened, leading to tube obstruction and finally death in the acute stage of infection. A fourth similar patient died at operation later for closure of the meningocele. The other unsuccessful case was of a child with an aqueduct obstruction still alive two and a half years after attempts at drainage were abandoned. It was concluded that it was desirable to carry out repair

of a meningocele before drainage was attempted. The use of cortisone to prevent abdominal reactions appeared to have some value and in the past 18 months a four-week course of cortisone had been given post-operatively in all cases. In all 33 cases had been treated with 85% successful results.

The outstanding problem of the operation was how to allow for the child's growth. Leaving spare coils of tube in the lateral ventricle or abdomen was unsatisfactory and the use of telescoping drains had been unsuccessful. The natural stretch of the silicone tube might compensate for some degree of growth but it was hoped that many of the cases might stabilize after a period of drainage. If necessary there was no reason why the procedure should not be repeated when the child outgrew the tube.

The operation probably had some value in post-inflammatory cases where a spinal block or raised intracranial pressure had developed. It was even possible in the active stages of tuberculous meningitis and no evidence of peritoneal involvement had followed such drainage. Eight such patients had been treated, seven of whom were still alive, and three further patients in an inactive phase had been treated, of whom two were still alive. Nine cases of pyogenic meningitis had been treated of which seven were still alive. Further conditions considered for this operation were subdural haematomata, pseudo-meningocele, pseudo-tumour cerebri, brain-stem tumours, and those cases where ventriculo-cisternostomy had failed.

BOOK REVIEWS

Handbuch der speziellen pathologischen Anatomie und Histologie. Edited by F. Henke, O. Lubarsch, and A. Rössle. Vol. XIII: **Nervous System**, edited by W. Scholz. (Section 2, parts A and B. pp. 2902; 1199 figures. DM. 859.50.) Berlin: Springer-Verlag. 1958.

The appearance of section two completes the 13th volume of the Henke-Lubarsch Handbook. Part A (pp. 1,325) deals solely with inflammatory disease of the central nervous system. The principal contributions are from Ludo van Bogaert, of Antwerp, who writes on the encephalitides and poliomyelitis; Hans Schleussing, of Munich, on meningitis; Gerd Peters, of Bonn, on multiple sclerosis and other demyelinating diseases; Ernst Sträussler, of Vienna, and O. Gagel, of Nuremburg, on neurosyphilis; and S. Scheidegger, of Basle, on tuberculosis, malaria, mycotic infections, and leprosy.

Part B (pp. 1,576) contains massive contributions from three authors: F. Erbslöh, of Munich, who writes on the neuropathological manifestations of various systemic diseases, including endocrine and blood disorders; Angel Pentschew, of Washington, on the intoxications and deficiency disease; and Hans-Joachim Colmant, of Bonn, on the various forms of motor neurone disease.

The Henke-Lubarsch Handbook is uniquely huge. Volume 13, which covers the pathology of the nervous system, consists of seven large books (of which the two parts under review are the largest), occupies 14½ inches of shelf space, weighs 35 lb. and costs about £206 10s. It is, and is likely to remain for several years, the major work of reference for neuropathologists all over the world—if they are fortunate enough to have access to it.

Pharmakopsychologie und Psychopathologie. By Wolfgang de Boor. (Pp. xi + 291. DM. 39.60.) Berlin: Springer-Verlag. 1956.

Much gratitude is due to anyone who undertakes the tedious labour of compiling an annotated bibliography of a rapidly expanding scientific field. Dr. de Boor has carried out this arduous task, as part of his effort to produce a compendium of "pharmaco-psychology". In order to keep his text within manageable limits, he has had to select from the vast literature; it is sometimes possible to disagree with his choice, but on the whole a balanced and informative picture is offered of the state of knowledge up to 1954. The chief defects are the relatively inadequate coverage of publications in English, and the lack of critical evaluation in the accounts of what individual workers have reported: these defects are particularly evident in the section on alcohol. Dr. de Boor hopes that this edition of his book will be the first step towards a complete review of the relevant material, carried out by a team of experts: the development of the subject, however, points to the need for a series of yearbooks rather than for a comprehensive treatise.

The Relationships Between Electroencephalographic and Psychological Data in Normal Adults. By P. F. Werre. (Pp. vii + 152 + 9 figures, 3 tables. Fl. 15.-.) Leiden: Universitaire Pers. 1957.

The author of this beautifully printed monograph evidently collected and examined his electroencephalographic data with loving care, while treating his psychological data with casual brevity. More than half of his text is devoted to a survey of the literature; of the remainder, in which he describes and discusses the observations made on 30 normal subjects, very little is concerned with the psychological tests and their detailed results. The treatment of these results is primitive, so that the reader has no means of judging whether the author's tentative conclusions about the relation between electroencephalographic and personality variables are warranted.

Methods of Group Psychotherapy. By Raymond Corsini. (Pp. xi + 251. 49*s*.) London: McGraw-Hill. 1957.

Group psychotherapy has developed in a haphazard way which makes it difficult to trace and know its various current forms. Dr. Corsini has here provided an impartial though not uncritical guide. In the first half of his book he details the history, theory, and procedures of group psychotherapy, with additional chapters on the desirable characteristics of the group therapist and on the evaluation, such as it is, of the various methods. The second half of the book offers verbatim samples of what goes on in four kinds of group treatment—the approximately psychoanalytic, the non-directive, the family-counselling, and the psychodramatic varieties. Though the review of the literature ends in 1955, it is fair and comprehensive, and shows keen awareness of those crucial questions about technique, indications, and modus operandi, which remain unanswered.

The Early Diagnosis and Treatment of Acoustic Nerve Tumors. By J. Lawrence Pool and Arthur A. Pava. (Pp. viii + 161; 33 figures. 42*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois; Charles C. Thomas. 1957.

This monograph provides a comprehensive review based upon a large personal experience and a knowledge of the literature. Although in the majority of cases the diagnosis can readily be made, in a proportion of patients with an evident intracranial tumour, the possibility that the tumour is acoustic is not even entertained. Such cases are described in this book and emphasis laid upon the need for careful tests of hearing and of labyrinthine function. It is in the attention to the disturbances of function of the acoustic and trigeminal nerves that early diagnosis can be achieved and the use of the word "early" in the title of this book implies an emphasis which is hardly present. Operative treatment is discussed in detail and the pros and cons of partial and of total enucleation carefully set out. It is a pity that this important section of the book has not been provided with better illustrations. Neurosurgeons will be interested to learn that tracheotomy is performed so frequently, often as a precautionary measure against anticipated respirator complications. The book will be of value to all neuro surgeons, and neurologists and otologists will find muc of interest in it. It provides a vivid commentary upon th progress made in neurological surgery since Cushin wrote in 1917 that "the foolhardiness of attempting total extirpation was not yet fully realised".

Mental Seduction and Menticide: The Psychology of Thought Control and Brainwashing. By Joost A. M. Meerloo. (Pp. 324. 21*s*.) London: Jonathan Cape. 1957.

False confessions, traitorous submission, acceptance of abhorrent beliefs—these evidences of what tyranny, torture, and ruthless indoctrination can achieve are miserably well known to our generation. Since the techniques used to bring about such results are patently psychological, and are reputed to be applications of what is known about conditioning, suggestion, motivation, and other such mental processes, it was inevitable that some psychiatrists, as experts in morbid psychology, would offer interpretations of what happens to individuals and to communities who use or who suffer these criminal techniques. Unfortunately their explanations commonly outrun the available facts, and become speculative musings or doctrinaire pronouncements. Dr. Meerloo's book is a tract for the times, drawing attention not only to the dangers of "brain-washing" and coercion but also to unobtrusive interference with our thoughts and feelings by mechanization, the growth of bureaucracy, and social pressures. He surveys all this from clinical, psychoanalytical, and Pavlovian standpoints. His outlook is liberal and his survey broad, though not penetrating: it would be more profitable reading for optimists than for cynics. There is relatively little technical jargon in this book, but at times the author tumbles into the pitfall, as when he tells us that "totalitarianism is man's escape from the fearful realities of life into the virtual womb of the leader": or that "Moloney compares this sudden yielding with the theophany or kenosis (internal conversion) as described by some theological rites".

Deafness, Mutism and Mental Deficiency in Children. By Louis Minski. (Pp. 82; 13 figures. 12*s*. 6*d*.) London: Heinemann. 1957.

This is an unassuming account of the work done in a unit conducted by Dr. Minski for the differentiation of mentally defective from deaf children and others with defective speech. It makes no pretence at surveying the literature of the subject, or assessing the relative diagnostic value of the physiological and psychological tests employed. Though medical readers would require more detailed evidence than is set out in it, this little book serves a modestly useful purpose as a simple statement of current practice, based on personal experience.

Atlas d'Anatomie Stéréotaxique. By J. Talairach, M. David, P. Tournoux, H. Corredor, and T. Kvasina. (Pp. 294; 99 figures, 91 plates. Fr. frs. 9,000.) Paris: Masson. 1957.

This handsomely produced volume represents con-

clusions based upon an anatomical study of 90 post-mortem brains. In a number of these, parallel needles, aligned by passage through a perforated metal plate, were passed into the brain through the skull either at right angles to the sagittal plane or parallel to it. Radiographs were taken in each of these two planes after injection of contrast media into the ventricles. The calvarium was partially removed to allow access of fixative, and 24 to 48 hours later the needles were removed and the brain examined. The remainder of the series were fixed *in situ* and the series of needles inserted after removal from the skull. In all specimens, the space between the needles being known, it was possible to measure the length of the "base line" and the dimensions of any particular nuclear structure.

The "base line" chosen was that connecting the anterior and posterior commissures of the third ventricle and through each of these a perpendicular was drawn. The position of the "base line" was also indicated at each antero-posterior level.

Histological examination was carried out on 10 brains of the series and sections were stained for myelin only. The remainder were cut into 2 mm. slices. From this study the conclusion is drawn that the various diencephalic nuclei maintain a constant relationship to the base line whatever the individual variations in its length. Thus, for the thalamus, a rectangle, drawn in the lateral encephalogram, is enclosed by the base line, the perpendiculars through the commissures, and a line parallel to the base line through the summit of the thalamus in the floor of the lateral ventricle. The two dimensions of this rectangle may vary from case to case, but the coordinates of any one nucleus are stated to vary proportionately.

It has not proved possible to evolve a similar proportional method for the lateral dimensions which are, therefore, represented by standard values in the antero-posterior film.

For any one structure, areas or "zones of security", are plotted in the lateral and antero-posterior films which represent the mean areas, for the structure, common to all specimens studied.

It is to be noted that 10 brains (histologically studied) is probably too small a number upon which to base the claim that the diencephalic and sub-thalamic nuclei bear a constant relationship to the intercommissural base line, particularly as such a claim is at variance with the conclusions of other workers. Further, the statement appears in the text to the effect that the perpendicular through the posterior commissure always passes at the posterior limit of the centromedian nucleus of the thalamus, while in three illustrations portraying this level the partially or fully developed centromedian nucleus can be seen.

The atlas proper consists of a presentation of the lateral and antero-posterior zones of security for the thalamic, subthalamic, and hypothalamic nuclei as well as the basal ganglia. In addition, various lateral and antero-posterior levels are depicted for each structure. It would appear, however, that this section cannot fairly be described as an atlas in that no level illustrated is accompanied by any indication of its position in relation to the commissures or base line.

The neurosurgeon for whom this book is primarily intended will certainly conclude that here is a technique that claims effectively to overcome the crucial problem of individual variation. The validity of this claim is unlikely to be called into question when the target is of the dimensions of the globus pallidus. For an individual thalamic nucleus, however, the surgeon may be employing a procedure whose real accuracy is limited by the restricted nature of the anatomical investigation upon which it is based.

L'Encéphalographie Fractionnée. By Giovanni Ruggiero. (Pp. 510; 288 plates. Fr. fr. 13,500.-.) Paris: Masson. 1957.

Encéphalographie Fractionnée describes the experiences of the author using this method of radiological examination in over 600 patients. The technique is now well known and follows those described by Robertson and Lindgren. This, however, is the first book in which extensive descriptions of technique, complications, and appearances of abnormalities, particularly in the posterior fossa and basal cisterns, have been recorded. For these reasons alone the book is particularly valuable. In addition it is beautifully illustrated with radiographs and line drawings, and in particular contains many tables summarizing the findings. The latter features make the book reasonably easy to understand even if the reader's knowledge of French is not extensive, but it is to be hoped that an English edition will be published. If this is done such a book will certainly be widely read by English speaking neurosurgeons, neurologists, and neuroradiologists.

La Physiologie et la Physiopathologie du Cervelet. By A. Kreindler and M. Steriade; Foreword by P. Mollaret. (Pp. 308; 87 figures. Fr. frs. 3,200.-.) Paris: Masson. 1958.

This book comes from the Pavlov Institute of Neurology in Bucharest and is a welcome though ambitious attempt at a complete account of the physiology of the cerebellum and its disorder by disease, a herculean task for any author, which, in this case, very nearly succeeds.

The book begins with a discussion of the phylogenesis, morphology, and histology of the cerebellum which is excellent and well illustrated. The remainder of the book is a combination of a critical review of the literature (both eastern and western) with accounts of the authors' own experience of human cerebellar lesions and of cerebellar ablation and stimulation in mammals. Chapter by chapter the relationship of the cerebellum with the spinal cord, the brain-stem, vestibular apparatus, and cerebral cortex are authoritatively discussed. When describing deficits of function, however, the authors are somewhat obsessed and overwhelmed at having to describe the "signs" so beloved by continental neurologists as the empirical necessity for diagnostic localization. Few of these remnants of Salpêtrière dogma are used by English neurologists today because, though the many reflex changes of cerebellar dysfunction are well

recognized, each change may be determined by a common disorder of function of the postural reflexes.

We would expect any work originating in "L'Institut de Neurologie I.P. Pavlov" to correlate changes in conditioned reflexes with the experimental lesions, and in this we are not disappointed, even though it is rather a short account tagged on to the end of the chapter on the cerebral-cerebellar relationships.

The final chapter on general theories about cerebellar function is disappointingly short and fails to summarize or amalgamate the experimental and review material. This reader is surprised that any account of posture and its disorders can be written without even mentioning muscle spindles, and it is unfortunate that Granit's brilliant work on the cerebellum is completely ignored.

Psychotherapy by Reciprocal Inhibition. By Joseph Wolpe. (Pp. xiv + 239. 40*s*.) London: Oxford University Press (Stanford University Press, Stanford, California). 1958.

In this book Dr. Wolpé presents a new method of psychotherapy. His argument is that only three kinds of processes are known which can bring about lasting changes in an organism's habit of response to a given stimulus situation: growth, lesions, and learning. Neurotic behaviour originates in learning, so that it is to be expected that its elimination will be a matter of "unlearning". He applied the known laws of learning to the special problem of neurosis and the technique of therapy by reciprocal inhibition emerged. The term "reciprocal inhibition" is borrowed from Sherrington who used it to describe the inhibition of one spinal reflex by another. The author expands its use to encompass all situations in which the elicitation of one response appears to bring about a decrement in the strength of evocation of a simultaneous response. The psychotherapeutic application of this is that if a response antagonistic to anxiety can be made to occur in the presence of anxiety-evoking stimuli so that it is accompanied by a complete or partial suppression of the anxiety responses, the bonds between these stimuli and the anxiety responses will be weakened.

Dr. Wolpe discusses his experimental work on cats in which lasting "neurotic" states had been induced and which could be "cured" by getting the animals to eat in the presence of progressively larger "doses" of anxiety-producing stimuli. He then discusses the application of the methods evolved to clinical practice, and gives the results of treating 210 neurotic patients. Of these patients, 39% were apparently cured and 50% were much improved. Only 3·3% were not benefited. These are impressive figures indeed and if substantiated the author has made a major contribution to the treatment of neurosis.

Polymyositis. By John N. Walton and Raymond D. Adams. (Pp. x + 270; 47 figures, 8 tables. 32*s*. 6*d*.) Edinburgh and London: E. & S. Livingstone. 1958.

This book comprises a review of the extensive literature on disorders of muscle, apart from dystrophy and purely infective conditions, followed by a very detailed analysis of 40 cases. A method of clinical classification which avoids much confusion in nomenclature is suggested. The present position of the pathological histology of muscular disorder is controversial and the significance of the author's findings on examination of biopsy specimens is presented with due reserve. They comment, "Although the clinical or pathological features alone may be insufficient for diagnosis, a combination of the two, with the aid of the electromyogram and biochemical tests, will, in our view, define and distinguish polymyositis as a specific syndrome in the majority of cases".

This account does much to clarify an apparently very diverse group of conditions and will be particularly helpful to clinicians in dealing with the difficult diagnostic and therapeutic problems which these disorders of muscle present.

Chronic Schizophrenia. By Thomas Freeman, John L. Cameron, and Andrew McGhie; Preface by Anna Freud; Foreword by T. Ferguson Rodger. (Pp. x + 158. 21*s*.) London: Tavistock Publications. 1958.

This psychoanalytic essay is based on observations made during two years at the Glasgow Royal Mental Hospital on 12 schizophrenic women and six schizophrenic men from the "chronic refractory" wards. The patients spent the day in a treatment centre provided with facilities for occupation. One of the authors also frequented a large "female refractory" ward where he would sit for one and a half to four hours a day watching, and would join the nurses at tea to discuss events in the ward. The authors also conducted, at the beginning, joint psychotherapy sessions. The method of recording and analysis used was not, as far as can be judged, systematic, but it consistently attempted to relate clinical observations to psychoanalytic theory. The authors recognize the risks in this procedure but defend it, in agreement with David Rapaport, on the ground that selecting patients' spontaneous utterances and making inferences from them is the method *par excellence* of clinical research. Whether this is so or not, it obliges the reader to choose between acceptance of the inferences because he too is a psychoanalyst or uncertainty about their validity because nothing has been done to test, refute or confirm them, they stand on their plausibility.

Anna Freud, quoting in her Preface the authors' description of their efforts as a "clinical, interpretative, and therapeutic study of schizophrenia", says that it is a "special merit of this book that it offers more than the sober title leads us to expect". As schizophrenia is the great riddle of psychiatry, this is indeed high praise. What the book mainly offers is a general account of the psycho-analytic conception of mental functioning and of the psychopathology of schizophrenia, perceptively illustrated by examples drawn from the authors' observations of their patients' disturbances of identity, perception, thinking and memory, and finally a description of how the nurses, at first insecure and anxious in their dealings with their patients, were gradually brought to understand them, talk freely to the psychiatrist about them, and become, in the authors' view, the vital factor in their recovery or otherwise. It is very clear that the

measures introduced by the investigators had an invaluable effect upon the nurses and were thereby beneficial to the patients, already far advanced in social deterioration and loss of self-respect: though other theoretical approaches (linked, as this was, with genuine interest, warmth, and humanity) have achieved similar, or, it may be, in some respects better results, the experiment here outlined should offer encouragement to psychiatrists and nurses confronted with the vast problem of chronic schizophrenia.

Neuritis, Sensory Neuritis, Neuralgia: A Clinical Study with Review of the Literature. By Robert Wartenberg; Foreword by W. Harris. (Pp. xii + 444; 13 figures. 68*s*.) Oxford University Press. 1958.

This is Dr. Wartenberg's last book, completed only a short time before his death. It is a most scholarly account of both the literature and his personal experience of disorders of the peripheral nerves, excluding traumatic lesions. It is therefore most valuable as a reference book. Clinical presentations are meticulously described. The discussions are almost entirely in terms of anatomy and histology. The work, therefore, is not only the final achievement of a distinguished neurologist; it is also among the last studies in classical neurology.

Die Hirngeschwülste in biologischer und morphologischer Darstellung, 3rd ed. revised. By K. J. Zülch. (Pp. vii + 249; 102 figures. DM. 27.80.) Leipzig: J. A. Barth. 1958.

Into this comparatively small book Professor Zülch, who is one of the world's leading authorities on tumours of the nervous system, has packed an enormous amount of information, much of which is not readily available elsewhere.

The first hundred pages are devoted to general considerations. The problems of classification, of histogenesis, and of aetiology are rapidly but thoroughly dealt with: statistics, with pictorial diagrams, are given for age, sex, and sites of predilection: and the general biological characters of brain tumours, including their secondary effects and their response to radiation, are discussed in some detail.

Eighty pages contain highly compressed descriptions of the various types of intracranial neoplasms, with excellent photographs of gross and microscopic specimens. The terminology used corresponds to that commonly adopted in this country, except that the term "spongioblastoma" is applied to the most benign type of astrocytoma—the cerebellar astrocytoma of childhood. A further 10 pages are usefully spent in consideration of other space-occupying processes, including parasitic cysts and granulomata.

The final section is concerned with the technical details of pathological investigation. There is a copious bibliography.

Altogether, this is a most businesslike monograph, and would repay translation into English.

Electroencephalographische Studien bei Hirntumoren. By Rudolf Hess; Foreword by Prof. H. Krayenbühl. (Pp. iv + 100; 8 figures. DM. 19.80.) Stuttgart: Georg Thieme. 1958.

This monograph reports the E.E.G. findings in nearly 700 patients with brain tumours seen in the Neurosurgical and E.E.G. Departments of the University of Zurich.

The report is mainly a statistical one on the varieties of abnormalities found in routine encephalography correlated with the site of the tumour. The work is very carefully done and reported in detail. No correlations with the type of tumour are attempted nor are any special E.E.G. methods included. There is only a brief discussion of theoretical problems.

The monograph is mainly of interest to electroencephalographers but gives a very clear and critical picture of the value of routine technique in the diagnosis of tumours.

L'Hydrocéphalie du Nourrisson. By Marc-Richard Klein in collaboration with Mme. L. Delegue, Mlle. J. Scharff, and Mme E. Bargeton; Foreword by Prof. Marcel Fevre. (Pp. 136; 37 figures. Fr. frs. 1,600.-.) Paris: Masson. 1958.

This short monograph on infantile hydrocephalus is based on more than 300 cases operated on at l'Hopital des Enfants Malades. Dr. Klein discusses the various causes of the condition, prefacing this with a description of the cerebrospinal fluid concentration. He favours operation at an early stage before serious damage to the brain has occurred and, judging by the photographs of smiling children with normal-sized heads following operation, he has successful results.

Fundamentals of Neurology, 3rd ed. By Ewart Gardner. (Pp. xi + 388; 154 figures. 40*s*.) Philadelphia and London: W. R. Saunders. 1958.

This is the third edition of a book by the Professor of Anatomy at Wayne State University College of Medicine, Detroit, designed to present the basic factors of the anatomy and physiology of the nervous system for the student starting his clinical work in neurology. Books of this type must, presumably, be of value for a number of them have appeared in the last 10 to 15 years and some, including this one, have gone through several editions. The subject is adequately and interestingly dealt with and there are a number of useful diagrams. There is a well selected list of books for more detailed reading, and a valuable and original feature, a glossary of terms used in neurology with their classical derivations.

Homosexuality, Transvestism and Change of Sex. By Eugene de Savitsch. (Pp. viii + 120. 12*s*. 6*d*.) London: William Heinemann Medical Books. 1958.

This small book gives the impression of having been put together hurriedly. Homosexuality and transvestism are discussed only superficially, and most of the book is devoted to the operation of "change of sex", by which the author means change of external genitalia by operation. The operation consists of three stages—castration, amputation of the penis, and the creation of a vagina, the last being regarded as somewhat of a " luxury".

The author describes three male transvestites who were so treated because they threatened suicide unless something were done about their unhappy condition, and had indeed made nearly successful attempts. The question of thus operating on transvestites is complex, and can be discussed in its moral, legal, and pragmatic aspects. The author's attempt to do so is all too superficial.

He emphasizes at all times the constitutional aspects of homosexuality and transvestism; but this chapter on transvestism, describing a few famous historical transvestites, such as the Abbé de Choisy and " Monsieur", the brother of Louis XIV, seems to stress rather the importance of training in the development of this condition. It is disappointing that there is no discussion of sex determination by chromosome study, a field in which some support for the author's dogmatic statements might possibly be found.

Autonomic Dyspraxia: An Hypothesis for the Mechanism of Psychosis, Neurosis and Psychosomatic Disease. By Brian G. Haynes. (Pp. viii + 122. 15*s*.) London: H. K. Lewis. 1958.

" Autonomic dyspraxia " is defined by the author as " disordered action of the autonomic control of the smooth-muscle and glandular structures throughout the body, the essential lesion lying in the hypothalamus, an emotional crisis being *sine qua non*."

In fact, what he is concerned with are the common psychoneurotic and psychosomatic states, all of which are attributed in a somewhat indiscriminate manner to autonomic imbalance. No new data are reported and no direct evidence of primary hypothalamic dysfunction is adduced.

In view of the well-established connotation of the term " dyspraxia " in clinical neurology, its use in the present context is to be regretted.

The Cerebrospinal Fluid: Production, Circulation, and Absorption. Ciba Foundation Symposium. Edited By G. E. W. Wolstenholme and Cecilia M. O'Connor. (Pp. xii + 335; 141 figures. 50*s*.) London; J. & A. Churchill. 1958.

This symposium includes much of the current knowledge of the anatomy and physiology of the cerebrospinal fluid and its pathways. The discussions at the end of each section will be chiefly of value to workers in the subject and to those contemplating experimental work involving cerebrospinal fluid or meninges. Many of the problems are clearly presented and much of the discussion is stimulating.

Foundations of Neuropsychiatry 6th ed., revised and enlarged. By Stanley Cobb. (Pp. ix + 305 + Index. 40*s*.) London: Baillière, Tindall and Cox. 1958.

The appearance of another edition of this well-known book testifies to its usefulness to students of neuropsychiatry. A vast field is covered but although the approach is imaginative it is at times superficial. A list of references at the end of each chapter, however, indicates to the student how he can explore the subjects more fully.

Viral Encephalitis. A Symposium. Fifth Annual Scientific Meeting of the Houston Neurological Society, Texas Medical Centre, Houston, Texas. Compiled and edited by William S. Fields and Russell J. Blattner. (Pp. ix + 225; illustrated. 52s. 6*d*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958

This volume contains a number of papers on various aspects of viral encephalitis presented at a symposium of the Houston Neurological Society in 1957. The rate of progress of the knowledge of this subject has been such that a series of up-to-date critical reviews by authorities in different fields might be expected to be of great value to neurologists wishing to keep abreast of current thought. The reader with such expectations will not be disappointed. The range covered is comprehensive, including accounts of the methods of identifying and distinguishing the neurotropic viruses, the practical problems of clinical and laboratory diagnosis, and a lucid account of the epidemiology of the western equine and St. Louis types of encephalitis. Dr. Knox Finley contributes a valuable study of the sequelae of these two diseases from which it emerges that severe and often irreversible damage to the brain is not uncommon and is especially frequent when the disease is acquired during the first year of life. A review of the pathology of viral disease in man characterized by nuclear inclusions by several authors, including Dr. Webb Haymaker and Dr. L. van Bogaert, with a complete bibliography, occupies half the volume, dealing mainly with the encephalitis known to be caused by herpes simplex, and the disease known as subacute inclusion encephalitis. The evidence for and against the identity of the acute and subacute varieties of this disease is discussed, the co-authors being unable to agree upon this question and presenting their arguments in detail. That the subacute form is the same disease as that originally described by van Bogaert as subacute sclerosing leukoencephalitis is accepted, the question whether this is a smouldering herpes simplex infection being left unanswered, after full discussion. Dr. Herald R. Cox in the final contribution discusses current trends in the control of neurotropic viral diseases and has much of interest to say about vaccination for poliomyelitis. He is uncertain whether the Salk vaccine will provide the eventual solution of the problem and emphasizes the importance of insuring that the occurrence of poliomyelitis is not being postponed from childhood until later in life, when the disease is more severe and paralysis and death are more frequent. He gives a detailed account of the recent attempts to produce immunity by the oral administration of attenuated live virus. This is a book which should be read by all neurologists, and possessed by those who can afford its price.

British Red Cross Society Mental Health Manual. By D. Stafford-Clark. (Pp. 86; illustrated.) London: British Red Cross Society. 1958.

This is an excellent little publication which will be most useful to all those concerned with instructing laymen in the elements of health and disease.

J. Neurol. Neurosurg. Psychiat., 1959, 22, 91.

THE TWO COMPONENTS OF THE GRASP REFLEX AFTER ABLATION OF FRONTAL CORTEX IN MONKEYS*

BY

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A grasp reflex was shown by Richter and Hines (1932) to result from experimental lesions in the pre-motor region (which they identified with area six of Brodmann) of the frontal lobes in adult monkeys. Reflex grasping in the monkey was later studied in more detail by Fulton and his associates in an effort to relate its occurrence to ablation of specific frontal areas and to analyse its nature at the periphery (Bieber and Fulton, 1933, 1938; Kennard and Fulton, 1933; Fulton, 1934). Since Janischewsky (1909) first described reflex hand grasping in a patient with organic brain disease, it has been the subject of many reports and several studies. Walshe and Robertson (1933) and Walshe and Hunt (1936) regarded the human grasp reflex as a purely proprioceptive reflex being devoid of visual or tactile elements, and a similar view of the simian grasp reflex was reached by Bieber and Fulton (1938). Seyffarth and Denny-Brown (1948) came to different conclusions for the human grasp reflex when they found that the adequate stimulus for it was a distally moving stimulus to certain areas of the palm. They were able to dissociate this triggering effect from the proprioceptive element. An essential sensory input for the reflex was derived from the skin and subcutaneous tissue of the palm, and this sensitized a secondary proprioceptive component when the stimulus stretched the long finger flexors. This secondary component reinforced and maintained the closing phase of the grasp initiated by palmar stimulation.

The large literature on reflex grasping shows many apparent discrepancies of observation and interpretation which are doubtless due to the confusion of terminology, lack of clear definition, and the failure to differentiate three distinct grasping automatisms (Seyffarth and Denny-Brown, 1948). In particular the lack of information regarding fixation of the upper limb during application of the stimulus to the palm leads one to suppose that shoulder traction had not been recognized as a potent stimulus, of itself, of reflex closure of the fingers (the traction response).

In this paper we shall refer to the grasp reflex as the finger flexion, with thumb adduction that occurs in response to a distally moving pressure contact applied to the palm preceding traction on the finger flexors, with the shoulder, arm, and forearm fixed. It is regularly present after frontal lobe lesions in the monkey. It is to be compared with the "instinctive grasp reaction" which is the response to a light stationary or moving tactile stimulus on any part of the hand and it consists of orientation of the hand into a position necessary for finger-thumb palpation and final grasping of the object. This reaction, which is independent of vision, is occasionally found in the normal monkey, though the more usual response to a light tactile stimulus to the hand is one of slight withdrawal (avoiding). The instinctive grasp reaction is released by frontal lobe lesions in the monkey. Finally, the traction response has to be clearly differentiated from the other two grasping automatisms. Traction response is reflex finger flexion and thumb adduction resulting from abduction and flexion or traction on the shoulder, and it can also reinforce the grasping automatisms outlined above. It is a synergistic effect of stretching the spastic muscles at the shoulder and it is present therefore in the thalamic monkey as Bieber and Fulton (1938) described. It is unaffected by deafferentation of the hand and arm, but not the shoulder (Twitchell, 1954) and is modified, as are stretch reflexes, by head and neck turning. Though it is not a true grasp reflex (as defined above), an animal rendered spastic experimentally and showing the traction response can learn to use it for a hooking type of grasping such as hanging from a bar. Later it may learn to project the arm to initiate the traction response of flexion of the fingers which can then be hooked around an object. The subsequent slight

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stretching of the spastic finger flexors by the object may then result in closing the fingers through a facilitated stretch reflex and so lead to a fixed resistance to opening of the hand. It is therefore necessary to distinguish the purely passive traction response from grasping as a positive act. The present experiments were designed to clarify the grasp reflex of monkeys after frontal lobe ablation and to demonstrate the part played by the efferent muscle spindle innervation (gamma motor fibres) in this reflex.

Methods

Monkeys (*M. cyamologous*) weighing between 2,200 and 3,000 g. were employed in this study. Their behaviour was watched for several days before operation and they were examined neurologically while strapped in a small chair designed to leave the limbs free while restraining the body. Under sterile conditions and nembutal anaesthesia (administered by the intraperitoneal route), the skull was opened by turning a left-sided bone flap. The central sulcus and the anatomical features of areas 4, 6, and 8 of Brodmann were identified. The left frontal pole was amputated, and areas 8 and 6 removed by subpial suction through small holes in the pia-arachnoid. The pia collapsed over the ablated areas. Much attention was given to the orbital surface and the cingulate (area 24) gyrus. The former was removed as far back as possible and the cingulate to the level of the medial limit of the central sulcus. After haemostasis had been secured, the dura was carefully repaired, the bone flap replaced and fixed by sutures in the galea. The muscles were closed in layers and the skin re-approximated by continuous subcutaneous silk suture.

By the next day the animals were usually quite active and at the end of a week the wound had healed sufficiently to allow of catching the animal in a net and strapping it into a special chair for neurological examination and experiment. The chair was provided with a wooden arm projecting at right angles to the chair-back and the animal's right forearm was fixed to this by strips of "elastoplast" around the elbow and wrist. A light rubber band was fixed to the finger tips and attached to a Grass strain-gauge myograph with sufficient tension to keep the fingers just extended. A small concentric needle electrode was placed within the flexor muscles of the fingers and lightly fixed there. The potentials picked up by this and the output of the strain-gauge were suitably amplified and displayed on a cathode ray tube which was photographed on moving paper by means of a Grass camera. The stimulus for the grasp reflex was provided by a small insulated metal strip fitted with electrical contacts. The strip was moved with moderate pressure across the palm beginning proximally and the initial contact with the palm was signalled automatically as was the increased resistance to movement as the stimulator encountered the flexing fingers. The grasp reflex so elicited was studied before and after injection of 1% procaine around the ulnar and median nerves at the wrist, and in separate experiments small quantities of procaine were injected into the flexor muscles of the fingers themselves. Finger jerks, response to pin prick in the palm, effects of turning the head and neck, and spontaneous struggling movements could be recorded.

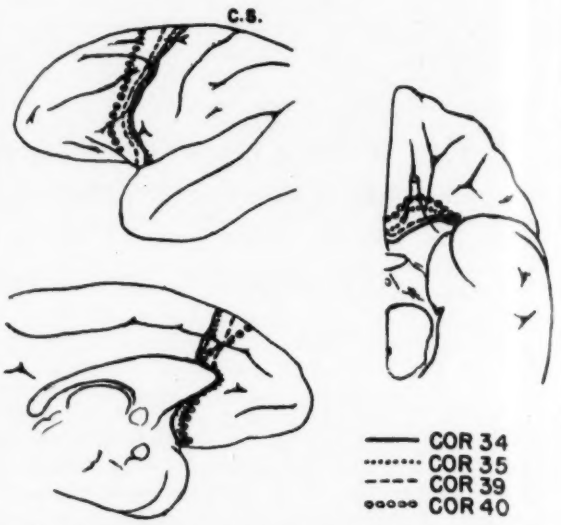


FIG. 1.—The extent of ablation of the left frontal lobe in the four monkeys described in the text, charted from the necropsy specimens. Where the ablation was bilateral it was approximately symmetrical. In animals COR 34 and COR 35 the entire cortex in front of the precentral sulcus was removed, whereas in animals COR 39 and COR 40 the precentral gyrus remained. C.S. is the central sulcus.

About six weeks after the first operation, the procedure was repeated in the right side of the head and the grasp reflex studied in both hands. The behaviour of the animals after frontal lobe lesions is to be reported at a later date. The extent of the ablations in the four animals discussed in this paper is shown in Fig. 1, and is drawn from the necropsy specimens which had been fixed *in situ*.

Results

Within one week of operation a grasp reflex was regularly elicitable from the palm contralateral to the cortical lesion and more facile avoiding responses from the homolateral limbs ("transcortical release"). When the animal was strapped into the experimental chair and its forearm fixed to the chair arm, a grasp reflex was still elicitable, though greater pressure of the moving object was now necessary to elicit the reflex every time. It was also necessary to see that the dorsum of the fingers and hand did not make contact with any part of the experimental chair, because tactile stimuli to the dorsum of the hand are powerful inhibitors of the grasp reflex. Neither the attaching of the fingers to a myograph through a light rubber band nor the insertion of a small coaxial electrode into the finger flexors had any significant effect on the grasp reflex.

By slowly moving the stimulating object across the palm on to the fingers using moderate pressure,

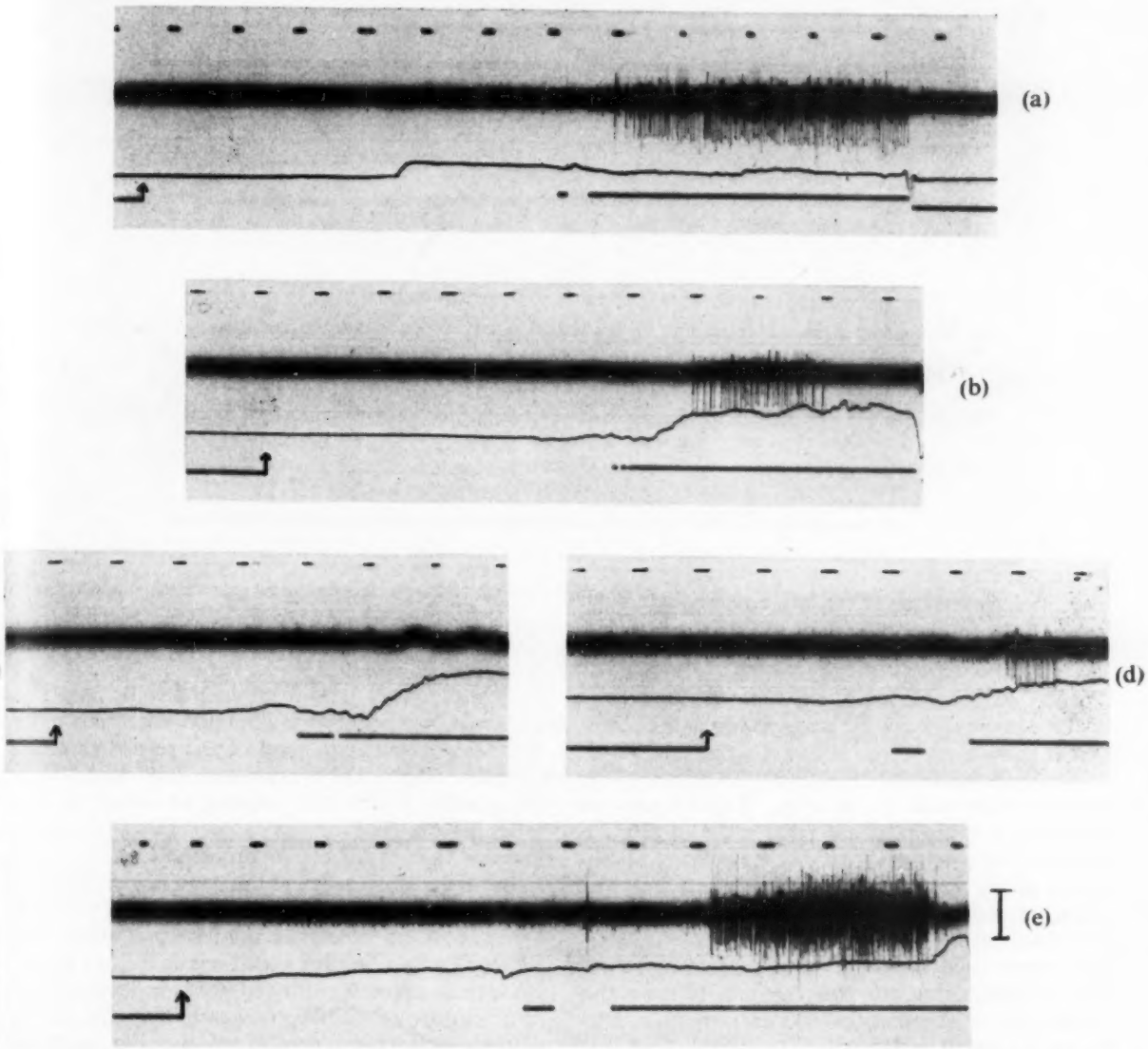


FIG. 2.—(a) The two components of the grasp reflex in the right hand of an animal (COR 35) with ablation of the left frontal lobe including areas 6, 8, and the cingulate gyrus. Electromyogram from finger flexors and myograph attached to finger. Stimulus applied to palm at the arrow; and at the continuous line during stretching of the finger. Time above in 1 seconds; (b) ten minutes after procaine infiltration around the ulnar and median nerves at the wrist (a small stretch reflex only remains); (c) twenty minutes later neither grasp reflex nor stretch reflex; (d) the same, with head turned strongly to the right when a small stretch reflex can be elicited in the finger flexors; (e) forty-eight minutes after the procaine injections, the grasp reflex begins to return. Voltage calibration in this and subsequent figures 100 μv.

a constant type of response in the finger flexors was invariably seen. Contact with the skin of the most proximal palm had at first no effect, but as the stimulus moved more distally rapid recruitment of small motor units was seen in the electromyogram and the fingers flexed slightly (Fig. 2a), particularly at the interphalangeal joints. They were in this state of partial flexion when the stimulus reached them and caused slight stretching of the finger flexors producing an outburst of large action potentials in the electromyogram and closing of the fingers on to the object. In some animals tonic grasping lasted for several minutes even when the stimulus was removed from the grasp, but nevertheless the outburst of large action potentials usually ceased when the stimulus no longer stretched the finger flexors. In this way, the two components, first cutaneous then proprioceptive, which provide the adequate stimulus for the grasp reflex, are demonstrable. Their relationship to each other may be analysed by

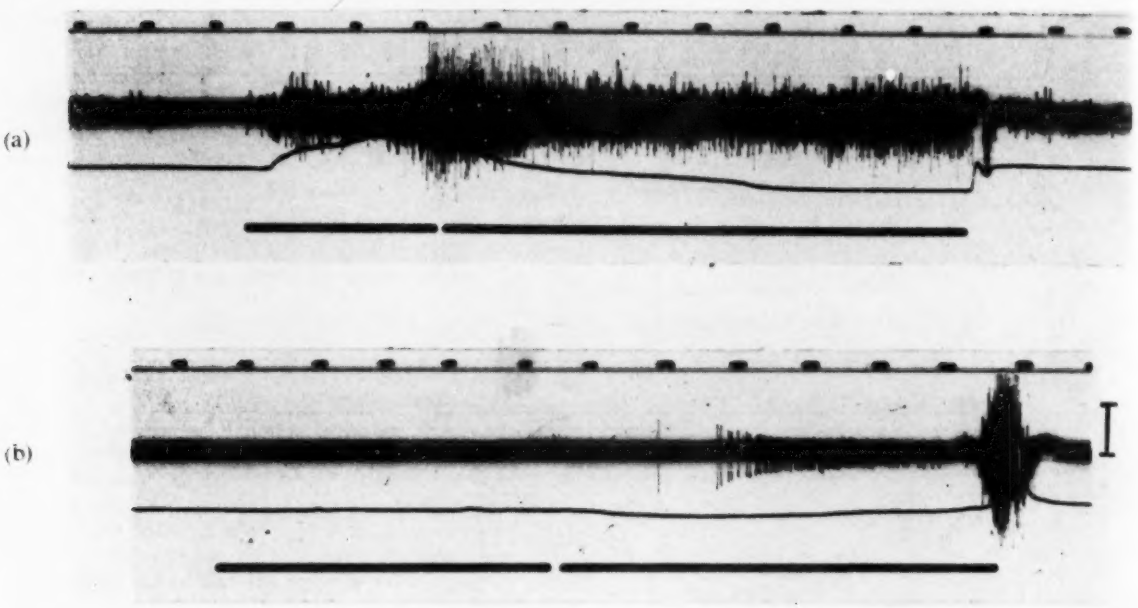


FIG. 3.—Electromyogram from another animal (COR 39) showing right grasp reflex. Palmar stimulus applied at beginning of first continuous line, stretching of the fingers during the second continuous line.
(a) Before procaine; (b) six minutes after procaine infiltration around ulnar and median nerves at the wrist. A stretch reflex elicited only on extreme stretching of the fingers. The record ends with a brief tetanic finger flexion of a spontaneous voluntary struggle by the animal.

injecting 1% procaine around both the ulnar and median nerves at the wrist so as to block the purely palmar stimuli.

Fig. 2b shows the state of affairs 10 minutes after procaine infiltration at the wrist. There is now no electromyographic response nor do the fingers flex when the object moves distally in the palm. Initially, stretch of the finger flexors has no effect but with greater stretch (as the stimulus reaches the middle and distal phalanges) a brief stretch reflex is seen. The fingers then exhibit a very mild resistance to passive stretch, but no grasping results from this proprioceptive stimulation. Twenty minutes later not even a small stretch reflex is elicitable (Fig. 2c), but if the head is turned strongly to the right (Fig. 2d) a little background activity is now seen in the electromyogram and a small stretch reflex from the finger flexors, but no grasp reflex. Forty-eight minutes after the procaine injection, the grasp reflex begins to return (Fig. 2e) with the small finger flexion in response to the cutaneous stimulation and the final tetanic closing phase being associated with stretching of the finger flexors.

In another animal (Fig. 3a), which showed a well developed tonic grasp reflex, the injection of procaine around ulnar and median nerves at the palm led to complete disappearance of the grasp reflex within six minutes of injection (Fig. 3b) though a feeble stretch reflex (a single unit in the electromyogram) was still present. The animal could still (and often did) "voluntarily" and maximally flex the fingers, as is shown by the outburst of action potentials in the electromyogram at the end of the record shown in Fig. 3b. When the procainized hand had lost its grasp reflex it was still possible to obtain a grasp reflex in the foot of the same side. This would indicate that the effect of procaine injected at the wrist on the grasp reflex of the hand is indeed a local effect and not due to the systemic effects of procaine.

In two of the monkeys a small strip of areas 6 and 8 immediately adjoining area 4 was purposely spared. Both these animals exhibited grasp reflexes but the tonic closure of the fingers was briefer than in the animals with more complete lesions. Fig. 4a shows such an example. Rapid recruitment of motor units is shown in the electromyogram in response to the cutaneous stimulation, and stretching of the fingers produces a relatively brief tetanic outburst which persists only as long as the fingers are stretched. Seven minutes after injection of 1% procaine around ulnar and median nerves at the wrist (Fig. 4b) a very little finger flexion occurs in response to the stimulus in the palm, but there is a stretch reflex which persists only as long as the muscles are stretched. It was possible in this animal to note that an area of skin overlying the heads of the second, third, and fourth metacarpals was particularly active in conditioning the stretch response in the finger flexors and this was still present 11 minutes after the procaine injection (Fig. 4c). By the seventeenth minute after

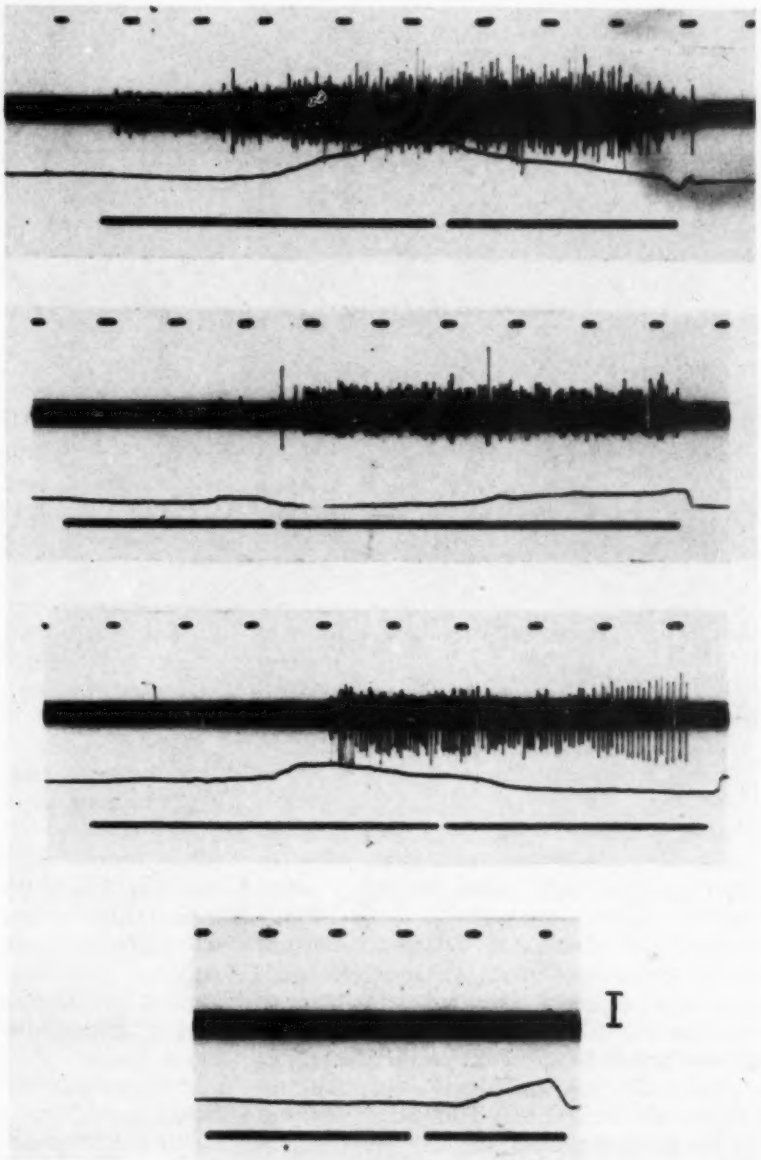


FIG. 4.—Animal with incomplete ablation of areas 6 and 8 (COR 40) left grasp reflex.

(a) Before procaine; large response to cutaneous stimulation, relatively little added to this by finger stretching; (b) seven minutes after procaine infiltration of ulnar and median nerves at the palm, no grasp reflex, a stretch reflex persists; (c) eleven minutes later. The skin over heads of second, third, and fourth metacarpals conditions an active stretch reflex in the finger flexors; (d) seventeen minutes later. No response to either cutaneous or proprioceptive stimuli.

injection of procaine both the grasp reflex and the stretch reflex had disappeared (Fig. 4d) and the skin of the palm now appeared to be quite anaesthetic, *i.e.*, the monkey did not respond to any form of finger or palmar stimulation.

These experiments demonstrate that the grasp reflex in the monkey is triggered off by cutaneous stimuli which condition the finger flexors in such a way that when the stimulus stretches these muscles then grasping occurs. Stretching the muscles alone without the initial cutaneous component fails to elicit the grasp reflex, and, indeed, if the cutaneous component is completely abolished by procaine then the stretch reflex of the finger flexors is absent.

In one animal showing a grasp reflex after ablation of the frontal lobe, including areas 6, 8, and cingulate, at a subsequent operation several weeks later, the ulnar nerve was divided at the wrist and a week later the median nerve. After division of the ulnar nerve a grasp reflex was obtainable only by stimulating the median distribution of the palm, and the fifth finger did not take part in the reflex and the fourth only partly. After the additional division of the median nerve, a grasp reflex could not be elicited even by a combination of finger stretching and head turning. There was, however, mild

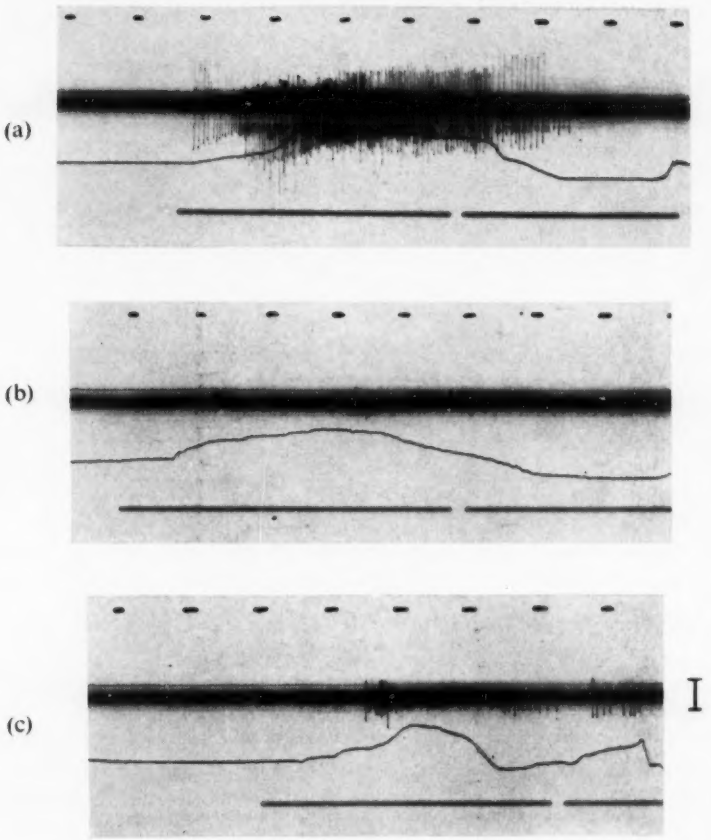
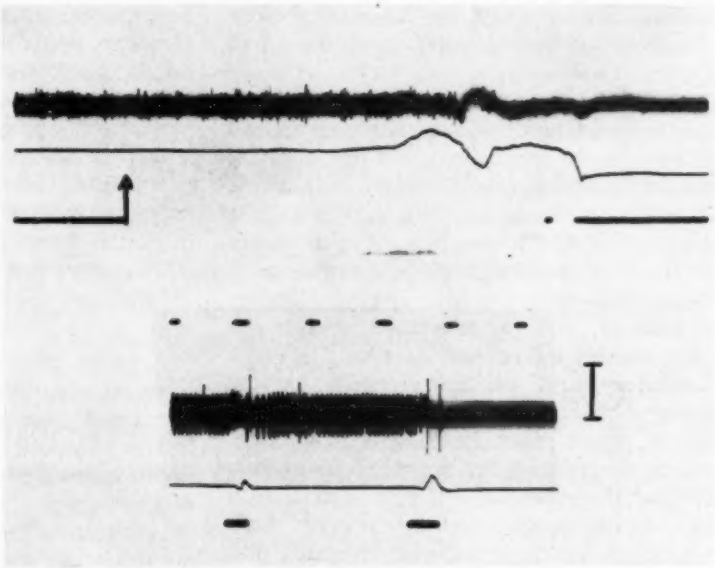


FIG. 5.—Cor 40 right hand (left areas 6 and 8 spared).

(a) The grasp reflex with little added to the cutaneous response by the proprioceptive stimulus; (b) two minutes after injection of 0·2 ml. of 1% procaine into the flexor muscles of the fingers. Very feeble flexion in response to cutaneous stimulation. Nothing added by finger stretching; (c) eleven minutes later, finger flexion begins but a very brief stretch reflex does not complete the act of grasping.

resistance to passive stretch of the fingers, *i.e.*, mild spasticity.

The response of a muscle to stretch depends not only on the excitability of its motoneurone pool but also on the sensitivity of its muscle spindles to stretch. Gamma motoneurones (fusi-motoneurones) in the spinal cord specifically innervate muscle spindles, and in this way their sensitivity can be controlled by the central nervous system. Stretch reflexes may be greatly exaggerated by the activity of gamma motor fibres, as for example, in decerebrate rigidity (Matthews and Rushworth, 1957a). It was thought possible that the cutaneous component of the adequate stimulus for the grasp reflex not only activated the motoneurone pool of the finger flexors causing partial finger flexion, but also activated the gamma motoneurones (fusi-motoneurones) of their muscle spindles, and thus conditioned the muscles to react tonically to stretching when the stimuli reached them. There is good evidence (Matthews and Rushworth, 1957b, 1958) that procaine tends to anaesthetize the gamma motor fibres of muscle spindles before either large motor fibres or large afferents and it was of interest therefore to observe the effects of injection of small quantities of procaine into the finger flexor muscles of monkeys after frontal lobe ablation. In every case the grasp reflex disappeared, usually within one minute of injection, and reappeared about 15 to 20 minutes later. Spontaneous movements by the animal during the period of absent grasp reflex were rare, but when they did occur they indicated, of course, that large motor fibres were still functional. Fig. 5a shows a grasp reflex in an animal which exhibited rather a short tonic grasping phase after the stimulus reached the fingers and stretched them. Two minutes after injection of 0·2 ml. procaine into the flexor muscles of the fingers (Fig. 5b), the fingers were very feebly flexed in response to the cutaneous stimulation and nothing was added to this by stretching the finger flexors. Eleven minutes after the procaine injection (Fig. 5c) a small finger flexion occurs in response to the cutaneous stimulus and a very small stretch reflex when the fingers are stretched. This is the type of "desensitized" stretch reflex one would expect to see if the gamma motor fibres to the spindles of the injected muscles had been blocked. The result indicates that most, if not all, the preliminary closing reaction as well as the proprioceptive component is mediated through the gamma system.



6.—Two animals with frontal lobe ablations sparing areas 6 and 8.
(a) COR 24. Heavy stimulus applied to palm at arrow. Very little recruitment of motor units, until stimulus reaches skin over metacarpal phalangeal joints when suddenly fingers flex followed at once by extension and silence in the electromyogram; (b) COR 40. Pin prick to the palm (signal below) during some activity of the finger flexors, brief grasp followed by avoiding of the fingers, prolonged after the second stimulus.

The poorly sustained tonic grasp of the animals with intact areas 6 and 8 is of some interest. It appears that excessive stretch on the fingers or excessive stimulus to the palm tends to inhibit grasping. In Fig. 6a a heavy stimulus was applied to the palm resulting in very little recruitment of motor units in the finger flexors and then suddenly a little flexion rapidly followed by extension of the fingers. Similarly in these animals pin prick to the palm caused a small finger flexion followed by extension, clearly seen if recordings were taken from the flexor muscles when there was some background activity (Fig. 6b). The usual response to pin prick in the palm of animals lacking completely areas 6 and 8 is one of finger flexion only (a brief grasp). It appears, therefore, that the sparing of areas 6 and 8 was responsible for the avoiding (extension) reactions in response to pin prick and heavy pressure. The avoiding reactions probably require the presence of areas 6, 8, and 24 for their full development (Denny-Brown, 1951).

Discussion

The grasp reflex after frontal lobe lesions in the monkey occurs as a result of a combination of cutaneous and proprioceptive stimulation. Of these, the cutaneous component is the essential initiator of the reflex and without this proprioceptive stimulation is ineffective. This is in complete agreement with the results of Seyffarth and Denny-Brown (1948) on the human grasp reflex. The opposite opinion of Bieber and Fulton (1938) that the grasp reflex in the monkey following frontal lobe lesions is a postural mechanism independent of cutaneous sensory influx is almost certainly due to the confusion between the "traction response" and the "grasp reflex". This may also account for the results of Walshe and Robertson (1933) and Walshe and Hunt (1936) for human grasping responses. Our own experiments clearly show that when palmar sensation is abolished in the monkey by either procaine infiltration at the wrist or by actual section of ulnar and median nerves, then the grasp reflex cannot be elicited.

Palmar stimulation by a distally moving object causes some initial finger flexion (at interphalangeal joints particularly), but the long finger flexors are rendered hypersensitive to stretch so that when the stimulating object stretches them the fingers will close on it. This overactive stretch reflex is almost certainly due to activation of the gamma motoneurones (fusi-motoneurones) which innervate the muscle spindles of the finger flexors causing their stretch receptors to become particularly sensitive. The local anaesthetic procaine, when placed around a muscular nerve, blocks gamma motor fibres in preference to either large motor fibres or large sensory fibres (Matthews and Rushworth, 1957b). The injection of very small quantities of procaine into the finger flexors rapidly abolished the grasp reflex, without necessarily having an effect on the power of contraction of those muscles. The integrity of gamma motor fibres to the muscle spindles of the finger flexors is shown to be necessary, not only for the final proprioceptive response of the grasp reflex, but also for the tactile facilitatory mechanism (closing phase) that prepares the finger flexors for stretch. The closing phase may thus be considered

a gamma response of which the facilitatory (subliminal) aspects are much wider than the small finger flexion.

The grasp reflex may be demonstrated in cats with high spinal lesions (Denny-Brown, Rushworth, and Saenz-Arroyo, to be published) and its essential factors are therefore a spinal reflex employing simple segmental pathways. In the cat, also, section of ulnar and median nerves at the wrist abolishes the grasp reflex, but the digits now exhibit a mild resistance to stretch, *i.e.*, they have become spastic (Denny-Brown, Twitchell, and Saenz-Arroyo, 1949). It appears that sensory influx from the fore-paw has a mixed inhibitory and excitatory effect on the motoneurone pool of the finger flexors; in the circumstances, when reflex grasping is prominent, the proprioceptive reflexes are depressed (or rather, dominated) by the cutaneous afferent system until a specific moving tactile stimulus triggers their release. It can be demonstrated experimentally that the reflex effects of median nerve stimulation at the wrist is, indeed, a complex mixture of inhibition and excitation on limb muscles with a tendency to produce extension of the forelimb (Denny-Brown and Liddell, 1928).

In one monkey experiment when the ulnar and median nerves were separately sectioned at the wrist, the fingers at first showed no increased resistance to passive displacement until four or five days after the second operation when they exhibited very mild spasticity with increased finger jerks. An increased stretch reflex of the finger flexors was never seen after procaine infiltration at the wrist, and the question then arises as to this difference between the experiments with procaine and those with nerve section. In both respects, however, the outcome is complicated by the avoiding response which is difficult to eliminate entirely by cortical ablation, and has frequently been found to be the reason for the transitory failure of motor reactions after cortical ablations (Denny-Brown and Chambers, 1958). The avoiding response has a much wider reflexogenous area in the upper limb than the grasp response. The situation is less complex in the animal with hemisection of the spinal cord and is being further examined in this context. The excitatory properties of the cutaneous stimulus have already been described in detail, but we have not so far considered any inhibitory activity on the stretch reflex mechanism which could be arising distal to the wrist. Possibly proprioceptors near the joints of the digits may inhibit the stretch reflex of the finger flexors, and the large afferents of such sensory organs would be expected to be very resistant to procaine. Stretch reflexes then would not be released by procaine infiltration but would be expected from total nerve section at the wrist. However, such a mechanism remains, at the moment, purely speculative.

The persistence of avoiding reactions of the fingers (extension) in response to pin prick or excessive stretch in animals with lesions of the frontal lobe, but sparing areas 6 and 8, again confirms the importance of these areas in the avoiding reactions of normal animals or animals lacking parietal lobes (Denny-Brown, 1951; Denny-Brown and Chambers, 1958).

Summary

A grasp reflex can be elicited in the contralateral hand after frontal lobe ablations (including cingulate gyrus and areas 6 and 8) in monkeys.

The adequate stimulus for it is a distally moving object causing stimulation first of the palm and then of the fingers.

Local anaesthesia of the palm with procaine abolishes the grasp reflex which cannot be elicited by proprioceptive stimulation alone (stretching of the fingers).

The palmar cutaneous component of the stimulus conditions the finger flexors for the subsequent stretch stimulus.

This conditioning results in partial finger flexion, especially at the interphalangeal joints (the closing phase), and also an increased stretch response of the muscles through activation of the gamma motoneurones (fusi-motoneurones) to the muscle spindles.

Nerve section at the wrist abolishes the grasp reflex but the fingers then show very mild spasticity.

Sparing of areas 6 and 8 allows some persistence of avoiding reactions in the hand to pin prick and excessive finger stretch and the grasp reflex is relatively poorly maintained.

One of us (G.R.) expresses his appreciation of a research travel grant from the Wellcome Trust and the National Spastics Society which made this work possible.

References

Bieber, I., and Fulton, J. F. (1933). *Amer. J. Physiol.*, **105**, 7.
——, —— (1938). *Arch. Neurol. Psychiat.* (*Chicago*), **39**, 433.
Denny-Brown, D. Unpublished observation.
—— (1951). "The Frontal Lobes and Their Functions." Ch. 2 in *Modern Trends in Neurology*, p. 13-89, ed. by A. Feiling. Butterworth, London.
——, and Chambers, R. A. (1958). *Res. Publ. Ass. nerv. ment. Dis.*, **36**, 35.
——, and Liddell, E. G. T. (1928). *J. Physiol.* (*Lond.*), **65**, 305.
Denny-Brown, D., Rushworth, G., and Saenz-Arroyo, L. To be published.
——, Twitchell, T. E., and Saenz-Arroyo, L. (1949). *Trans. Amer. neurol. Ass.*, **74**, 108.
Fulton, J. F. (1934). *Arch. Neurol. Psychiat.* (*Chicago*), **31**, 221.
Janischewsky, A. (1909). *Rev. neurol.*, **17**, 823.
Kennard, M. A., and Fulton, J. F. (1933). *Brain*, **56**, 213.
Matthews, P. B. C., and Rushworth, G. (1957a). *J. Physiol.* (*Lond.*), **135**, 245.
——, —— (1957b). *Ibid.*, **135**, 263.
——, —— (1958). *Ibid.*, **140**, 421.
Richter, C. P., and Hines, M. (1932). *Amer. J. Physiol.*, **101**, 87.
Seyffarth, H., and Denny-Brown, D. (1948). *Brain*, **71**, 109.
Twitchell, T. E. (1954). *J. Neurophysiol.*, **17**, 239.
Walshe, F. M. R., and Hunt, J. H. (1936). *Brain*, **59**, 315.
——, and Robertson, E. G. (1933). *Ibid.*, **56**, 40.

J. Neurol. Neurosurg. Psychiat., 1959, 22, 99.

CONGENITAL HYDROCEPHALUS WITH DEFECTIVE DEVELOPMENT OF THE CEREBELLAR VERMIS (DANDY-WALKER SYNDROME)

Clinical and Anatomical Findings in Two Cases with Particular Reference to the So-called Atresia of the Foramina of Magendie and Luschka

BY

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Several reports of malformations affecting only or chiefly the cerebellar vermis can be found in the literature. As a rule the vermis has not been fully developed, particularly its posterior part, and it is a striking feature that this defect has usually been combined with internal hydrocephalus. It appears from the descriptions given in the literature that these cases have been remarkably similar in their pathology as well as in their clinical manifestations and course. We have been able to record altogether 30 human cases, namely those of Fusari (1891-92), Rossi (1891 and 1892, two cases), Woskressenski (1911), Dandy and Blackfan (1914), Dandy (1921, two cases), Lyssenkow (1931), Pines and Surabaschwili (1932), Castrillón (1933), Scarff (1933), Sahs (1941), Cohen (1942), Taggart and Walker (1942, three cases), Shryock and Alexander (1943), Walker (1944), Brodal (1945), Sidenberg, Kessler, and Wolpaw (1946), Coleman and Troland (1948, two cases), Schwarzkopf (1950), Benda (1954, three cases), Maloney (1954, two cases), Gibson (1955, two cases). Similar malformations have been reported in animals by Lesbre and Forgeot (1905, calf), Bertrand, Medynski, and Salles (1936, dog), Dow (1940, two cases in dogs), Verhaart (1942, cat), Brodal, Bonnevie, and Harkmark (1944), and Bonnevie and Brodal (1946, in a strain of mice).

In spite of the similarity of the findings in these cases we disagree with regard to the mechanism underlying the development of the anomalies, which by some is held to be a congenital atresia of the foramina of Magendie and Luschka. This problem will be discussed in the present paper with reference to the findings in two cases together with observations made in a strain of mice presenting a hereditary type of the same malformation (Brodal and others, 1944; Bonnevie and Brodal, 1946).

Case Reports

Case 1.—A.B.G. A girl aged 4 years, was born on September 24, 1945, and died on September 12, 1949. (R.H. 861/49, O. 224/49, H.I. 14/49.)

History.—The patient was born five weeks prematurely, and weighed 2,000 g. at birth. The delivery was uneventful. Growth was slow until she was 6 months old, but since then her development has been in all respects satisfactory.

During the six months before admission her mother had noticed that the child had occasional fits, in which peculiar movements of the eyes, staring gaze, and dilated pupils were associated with absent-mindedness, though she replied when spoken to.

Since July 8, 1949, she complained of headache and abdominal pain, usually accompanied by nausea and vomiting. After July 20 she became drowsy and responded poorly when spoken to. Her gait grew unsteady; twice there had been signs of diplopia. From July 17, she had increasingly frequent seizures, up to nine in 24 hours, each lasting for two or three minutes. During these she displayed opisthotonus with extension of the legs and flexion of the arms which showed rhythmic, jerking movements. She appeared to be unconscious during these seizures, which were regularly followed by sleep.

Clinical Examination.—On admission to the Neurological University Clinic, Oslo (July 26, 1949), the patient was drowsy and unresponsive. Her head was retracted and tilted to the left. The head circumference was 51 cm. (average for her age 49 cm.). The frontal and parietal tubera were large. Body weight was 12 kg., height 122 cm.

There was bilateral papilloedema and swelling of the optic discs of 4 and 3 diopters. There were no ataxia or spontaneous movements, no involuntary movements, but slight muscular hypotonia. Kernig and Brudzinski signs were positive. Tendon reflexes were weak but symmetrical, except for the patellar reflexes which were both absent. Abdominal and plantar reflexes were

normal. A general examination, including laboratory tests of blood and urine, gave normal results. The Wassermann test was negative in blood. A radiograph of the skull showed wide coronal sutures.

Since a medulloblastoma of the cerebellum was suspected, the patient was given daily *x*-ray treatment starting on July 28. On September 6 ventriculography was done and 250 ml. of cerebrospinal fluid was removed, which had a normal content of cells, protein, and glucose. The ventriculograms showed enormously dilated lateral ventricles (Fig. 1), a large third ventricle, and a markedly dilated aqueduct of Sylvius. The contours of the fourth ventricle could not be made out, but there was a large air-filled space under the elevated tentorium cerebelli, suggesting a defect in the cerebellum.

After ventriculography she deteriorated, her temperature rose, and on the sixth post-operative day reached 41·3° C. She died the same afternoon.

Anatomical Investigation.—Necropsy was performed by Dr. J. Cammermeyer. Pathological findings were confined to the brain.

The leptomeninges appeared to be somewhat thickened. The cerebellar hemispheres were separated by what appeared to be an enormously enlarged fourth ventricle covered by a membrane uniting the cerebellar hemispheres. The brain, including the cerebellum, weighed 900 g. After fixation in formalin it was sent to the Anatomical Institute for further examination.

The cerebral hemispheres appear grossly normal except for some flattening of the convolutions and ventriculostomy wounds in both occipital lobes. The floor of the third ventricle bulges considerably.

Coronal sections reveal severe internal hydrocephalus (Fig. 2) most marked on the left. The third ventricle is abnormally wide, the interventricular foramina of Monro and the aqueduct are dilated, the thalamus and basal ganglia are displaced laterally and appear flattened and somewhat reduced in size.

The thickness of the cerebral cortex is reduced throughout, the corpus callosum has a maximal thickness of 2·5 mm. and the anterior, posterior, and habenular commissures appear as cords.

From the posterior aspect (Fig. 3a and b), the two cerebellar hemispheres are separated by a wide cleft bridged by a thin ruptured membrane (Fig. 3a). Anteriorly the membrane bears a tongue-like structure, consisting of some transversely running cerebellar folia.

Retraction of the two halves of the membrane exposes the floor of the fourth ventricle (Fig. 3b). Posteriorly no trace of a vermis is seen, but anteriorly it is represented by an unpaired prominence (x in Fig. 3b), convex in the rostro-caudal as well as the lateral direction but having a small transverse furrow (y in Fig. 3b). The under surface of this prominence can be followed rostrally to the caudal opening of the aqueduct, while its upper surface is covered with cerebellar folia. The most posterior of these form the tongue-like mass of folia which can be seen from the outside (V in Figs. 3a and b). These relationships become clearer after the cerebellum and brain-stem have been cut mid-sagittally (Fig. 4). Upon careful dissection, the folia of the preserved anterior part of the vermis can be identified by their connexions with parts of the hemispheres (see below). Extending from the anterior part of the vermis is a thin anterior medullary velum which is attached to the brachia conjunctiva.

The ventricular surface of the vermis (x) is separated on each side by a shallow sagittal sulcus from a smooth, somewhat smaller prominence facing medially (z in Figs. 3b and 4) which macroscopically belongs to the hemisphere. This smooth prominence fuses ventrally with a bulging produced by the brachium conjunctivum (Bc in Fig. 4), posteriorly it extends onto the medial surface of the hemisphere. The hemispheres are smaller than normally, but all lobules can be identified. The upper surface of the cerebellum is more anterior than normally, and the vermis overlies the superior colliculi.

The membrane covering the fourth ventricle is thin, more or less translucent, and contains fine vessels. It appears to be attached to the cerebellum along a laterally curved line which passes approximately in a rostro-caudal direction on the dorsal (posterior) surface of each hemisphere (Figs. 3a and b and 5). When followed in a rostral direction, the line of attachment bends medially and ultimately reaches the tongue-like extension of cerebellar folia. Caudally the line of attachment also bends medially to the medial surface of the hemispheres, to reach the flocculus (Figs. 3b and 5), below which its most anterior point is found. Here a foramen of Luschka is present on each side, through which a tuft of the choroid plexus (Figs. 5a and b) protrudes. From the region of the foramen of Luschka the attachment of the membrane passes just inferior to the flocculus in a medial direction, reaches the lateral border of the medulla oblongata and follows this caudo-medially to meet its fellow from the other side in the midline caudal to the fourth ventricle. This line of attachment of the membrane is somewhat more lateral on the surface of the medulla than the taenia of the fourth ventricle in a normal brain.

On the ventral surface of the caudal part of the membrane, which extends across the cleft between the two cerebellar hemispheres, several distinct ridges of a choroid plexus are seen on both sides, coursing in a longitudinal direction (Fig. 6). From the caudal end of the lateralmost of these ridges a well developed strand of choroid plexus extends anteriorly, a few millimetres medial to the line of attachment of the membrane to the cerebellar hemispheres. The most anterior part of this plexus protrudes through the foramen of Luschka on both sides (Fig. 5a and b).

The pons and medulla oblongata show only minor changes. The medulla is transversely flattened but all normal structures can be identified. The pons is somewhat flattened, but is otherwise normal. In the mesencephalon the cerebral peduncles appear small, and the aqueduct is dilated. The cranial nerves are all present and appear normal.

Microscopical Investigation.—Pieces were removed for histological study from the membrane covering the fourth ventricle and from its line of attachment to the cerebellum and stained with haematoxylin-eosin. The left half of the cerebellum and the entire medulla oblongata and pons were embedded in paraffin and sectioned serially in the transverse plane. The right half of the cerebellum was cut in serial sections in the sagittal

FIG. 1

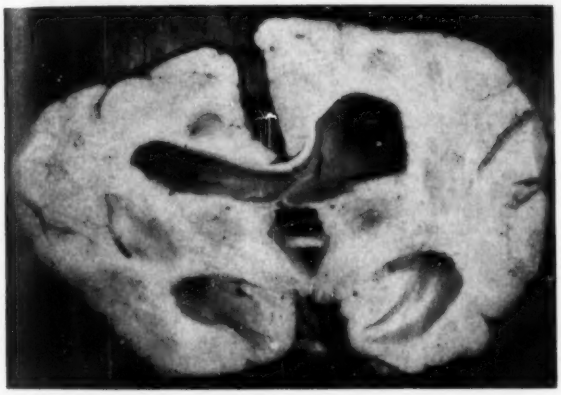


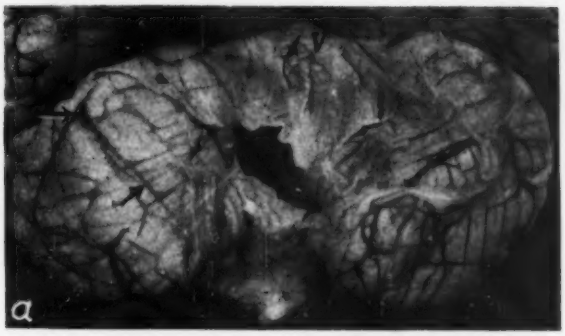
FIG. 2

FIG. 1.—Case 1: Ventriculogram showing dilatation of lateral and third ventricles and a large collection of air in the posterior cranial fossa below an elevated tentorium.

FIG. 2.—Case 1: The posterior part of the cerebral hemispheres seen from the anterior aspect following a transverse section at the plane of the mammillary bodies. The corpus callosum is reduced in thickness. The posterior and the habenular commissures extend across the dilated third ventricle.

FIG. 3.—Case 1: The cerebellum seen from behind, showing in (a) the ruptured membranous covering of the fourth ventricle. The line of attachment of the membrane on the left cerebellar hemisphere is indicated by arrows. In (b) the membrane is pulled aside to expose the fourth ventricle. In the midline is seen the ventricular surface (x) of the anterior part of the vermis. V: posterior part of vermis. To: tonsilla. z and y: see text.

FIG. 4.—Case 1: The right half of the cerebellum and brain-stem. The upper part of the membrane is kept raised by means of a pin to expose the smooth ventricular surface of the cerebellum with its prominences (z and Bc) described in the text. F.p.: primary fissure. To.: Tonsilla. y: Sulcus corresponding to the fastigium.



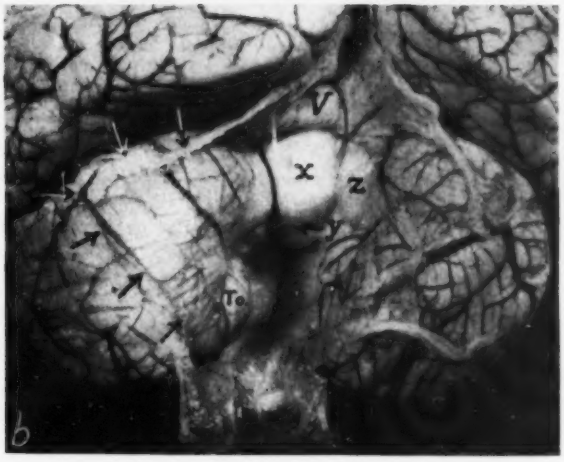


FIG. 3

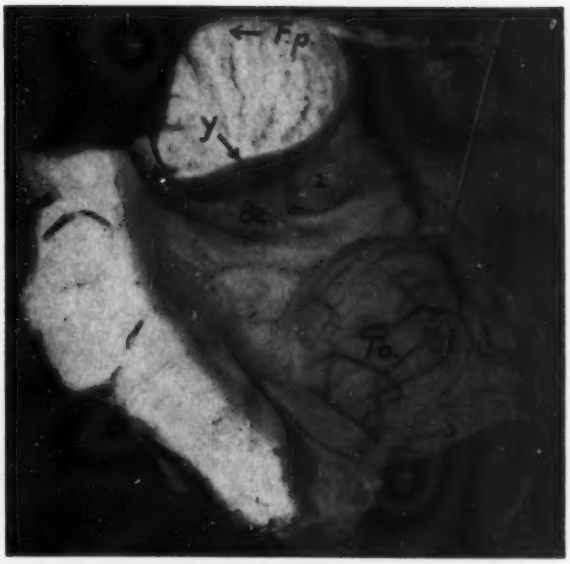


FIG. 4

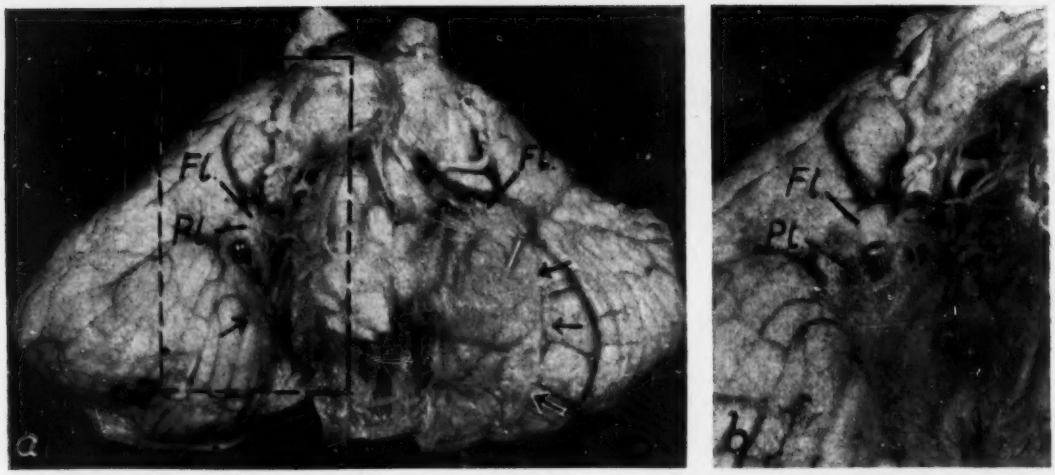


FIG 5.

FIG. 5.—Case 1: (a) Anterior view of the cerebellum and brain-stem to show the relations of the membrane and the patent foramina of Luschka. The line of attachment of the membrane on the left is shown by arrows. Pins are placed in the foramina of Luschka. Fl.: Flocculus. Pl.: Choroid plexus. (b) Enlarged view of the area outlined in (a) showing the choroid plexus (Pl.) protruding through the right foramen of Luschka.

FIG. 6.—Case 1: The posterior part of the translucent membrane drawn backwards (cf. Fig. 3b) to expose its inner surface with the ridges of choroid plexus (Pl.).

FIG. 7.—Case 1: Sagittal section through the vermis of the cerebellum. The folia and lobules of the anterior lobe in front of the primary fissure (F.p.), and the folium-declive-tuber (Fdt.) have an approximately normal configuration. The pyramis (Py.) and particularly the uvula (U) are elongated in the sagittal plane and not subdivided in their peripheral portions as usual. The nodulus (N) is flattened and extends as fragments of cerebellar tissue on the outer surface of the membrane. The eversion of the vermis leaves a faint groove only, indicating the fastigium (F), corresponding to the sulcus y in Fig. 4.

FIG. 6

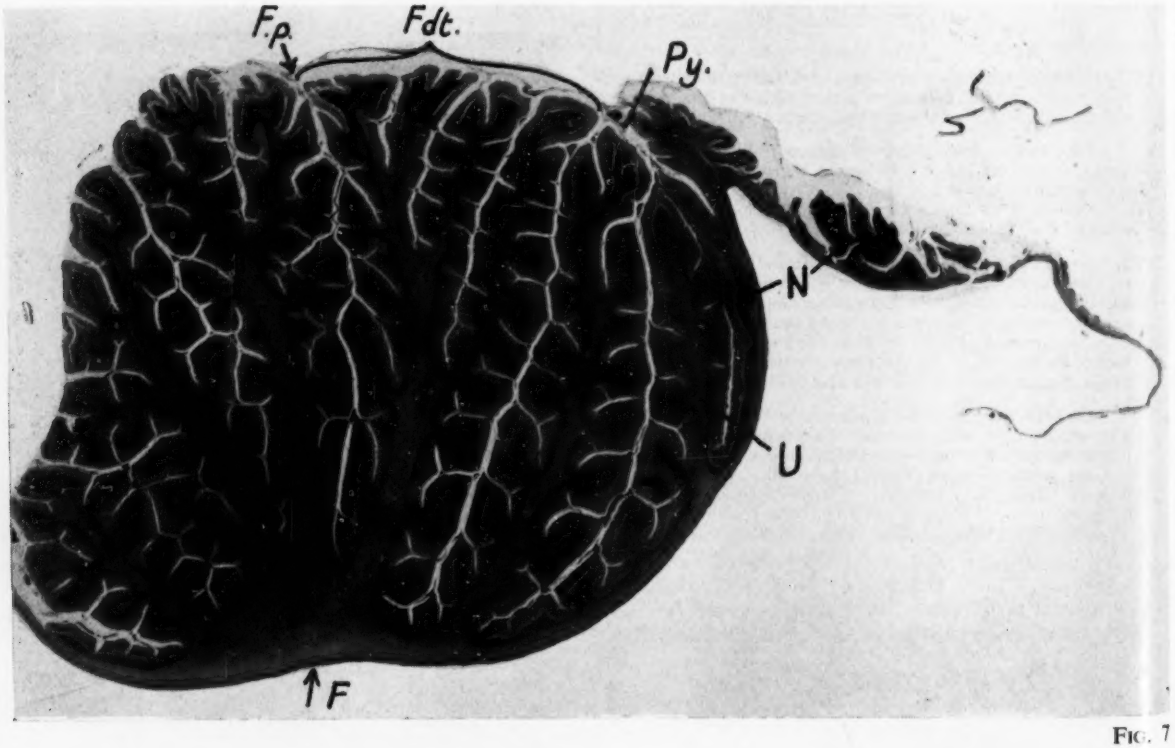


FIG. 7

plane. Every tenth section was mounted and stained with cresyl violet.

Microscopically the membrane covering the fourth ventricle is covered by ependyma on its ventricular surface and by loose connective tissue with small vessels on its outer surface. The ependymal cells are in places cuboidal, elsewhere flattened. Occasionally small tufts of connective tissue covered by ependyma protrude on the inner surface of the membrane. From the line where the membrane is attached to the cerebellar hemispheres (Fig. 3a and b) the ependymal lining of the membrane continues in a ventral direction and covers the medial surface of the cerebellar hemisphere, but is separated from this by a thin layer of connective tissue, which can be followed ventrally to the region where the folia of the hemisphere disappear. The outer, connective tissue layer of the membrane is continuous with the pial covering of the cerebellum.

The choroid plexus appears normal except that its arborizations are fewer and more slender than normal.

Study of the sagittal series of sections through the right half of the cerebellum establishes that all lobules of the vermis are present. But, while the lobules of the anterior lobe appear to be normally developed, those of the posterior lobe are more or less reduced in size (Fig. 7) and are abnormal in shape. In particular the nodulus is very irregular and flattened; in part it is stretched out on the outer surface of the membrane (Fig. 7). The fastigium is very faintly marked (F in Fig. 7) and corresponds to the fissure y seen on gross examination (Fig. 3b). The flattening of the ventral surface of the vermis is due to the elevation of the posterior part of the cerebellum above the floor of the fourth ventricle.

The cortex of the cerebellum is of normal structure apart from some minor aberrations in the malformed nodulus. On the ventricular surface the ependyma in some places shows the picture of "granular ependymitis".

The intracerebellar nuclei when studied in serial sections show some irregularities. The dentate nucleus is situated closely beneath the ependyma, underneath the prominence labelled z in Fig. 3b. Its regular band is not everywhere clearly outlined, and medially its band-like structure is lost. The medialmost cell aggregates of the intracerebellar nuclei may represent part of the dentate nucleus, but may also be rudimentary parts of the fastigial, globose, and emboliform nuclei which cannot be identified.

Histological sections through the pons and medulla show no substantial abnormality. The inferior olive, studied in detail, showed a possible reduction in size of the rostral part of the medial accessory olive.

Case 2.—R.S., a girl aged 7¾ years, was born on October 12, 1942, and died on August 31, 1950. (R.H. 556/50, O. 208/50, H.I. 7/50.)

History.—The child had been in good health and developed normally until February, 1950, when she began to complain of pains and stiffness in her neck and had a fit during which her body grew stiff and her gaze was staring. There were no convulsions. During the following three weeks she had moderate fever. In April

Fig. 8.—Case 2: Ventriculogram showing essentially the same features as in Case 1 (see Fig. 1).

the same symptoms recurred but again disappeared after some weeks. In July she again had two fits with stiffness of the body and extension of fore- and hindlimbs without loss of consciousness. She was admitted to the Paediatric University Clinic on July 15, from which she was transferred on July 31 to the Neurosurgical Division of the Neurological University Clinic.

Clinical Examination.—On admission the girl complained of headache, and particularly of pain in the neck on movements of her head. The neck was stiff and a "cracked pot" note was heard on percussion of the head. Both optic discs were choked with engorged veins, protruding some 4 diopters. There was paresis of the right abducent nerve, and signs of affection of both oculomotor nerves. There was general muscular weakness and atrophy with some spasticity in the legs, and signs of cerebellar ataxia. The tendon reflexes in the legs were very brisk, the abdominal reflexes weak and the plantar reflexes inverted. Laboratory tests of urine and blood were normal apart from an increased blood sedimentation rate. A chronic otitis was found on the right.

At ventriculography 200 ml. of cerebrospinal fluid was removed. Its protein content was normal but glucose and cells were slightly raised. The ventriculogram (Fig. 8) showed great dilatation of the lateral and third ventricles. In the posterior fossa below a markedly elevated tentorium was a large air-filled space. The cranial sutures were widened.

After ventriculography cerebrospinal fluid leaked through the left burr hole, and on the second postoperative day her temperature rose suddenly. In spite of treatment with aureomycin and penicillin her condition continued to deteriorate until she died 13 days later.

Anatomical Investigation.—Necropsy was performed by Dr. J. Cammermeyer. Apart from the brain no pathological alterations of significance were noted. The weight of the brain was 1,050 g. After fixation in formalin the brain was referred to the Anatomical Institute for further study.

On gross examination the leptomeninges over the base of the brain and medulla are covered with pus,

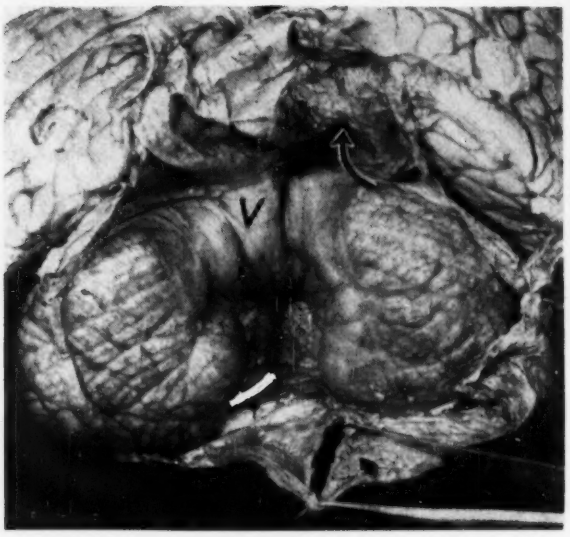


Fig. 9.—Case 2: Posterior view of the cerebellum with the enlarged fourth ventricle and the under surface of the vermis (V). Parts of the membrane, drawn aside, are visible, as well as its line of attachment. The entrance to the rostral sac-like evagination of the membrane is indicated by an arrow.

thickened and their vessels prominent. On transection of the cerebral hemispheres the lateral and third ventricles are considerably enlarged, although less than in Case 1. The commissures and the massa intermedia are elongated transversely. The aqueduct is dilated rostral to the inferior colliculus where it is narrowed. Otherwise the appearances of the cerebrum are as in Case 1.

The cerebellar hemispheres are driven apart, and connected rostrally only by what appears to be a reduced vermis (Fig. 9). The right hemisphere is a little smaller than the left, particularly in the region of the tonsil, which on the right shows indistinct foliations. The pathological alterations are otherwise in principle similar to these described in Case 1. The two cerebellar hemispheres are caudally connected by a membrane which is considerably thicker and more vascular than that in Case 1. Its torn ends can be brought together, and there can be no doubt that the membrane has originally covered the fourth ventricle. Its line of attachment to the hemispheres is approximately as in Case 1. However, from the right rostrolateral part of the membrane, caudal to its attachment to the vermis rudiment, a sac-like evagination extends in a rostral direction to the under surface of the corpus callosum. Above this evagination a vermis of reduced size connects the two cerebellar hemispheres. On the inner surface of the caudal part of the membrane is a somewhat underdeveloped choroid plexus. On account of the thickening of the membrane and meninges the foramina of Luschka cannot be identified.

Microscopical Examination.—This shows heavy infiltration of the leptomeninges, chiefly with polymorphonuclear and some mononuclear leucocytes. There is some perivascular cuffing of the pial arteries. In the right cerebellar hemisphere a well circumscribed abscess is found, measuring 2 × 1 × 1 cm. It is surrounded by a marginal zone of leucocytes and "foam cells". The abscess destroys part of the dentate nucleus in addition to white matter. Sagittal sections through the vermis show that all lobules are present, but as in Case 1 those of the posterior vermis are underdeveloped and abnormal. In sections through the pons and medulla oblongata the configuration of the major nuclei and tracts appear largely normal. A detailed study of the particular tracts and nuclei was not made.

The chief anatomical findings in these two cases may be summarized as follows: The entire ventricular system is considerably dilated. The tentorium cerebelli is elevated. The cerebellar hemispheres are separated caudally by a broadened fourth ventricle; rostrally they are connected by a vermis, which is somewhat everted and displaced rostrally. The vermis of the anterior lobe is normal, while posteriorly the vermis is underdeveloped. While all the usual lobules can be identified, the uvula and particularly the nodulus are smaller than normal and also have an abnormal configuration.

The caudal part of the roof of the fourth ventricle is formed by a thin membrane of connective tissue (pia mater) covered on its inner surface by ependyma. Its line of attachment to the brain-stem corresponds to that of the normal tela chorioidea, while its attachment to the cerebellum on macroscopical examination is found on the dorso-medial surface of the hemispheres. On microscopical examination, however, the ependyma on the inner surface of the membrane continues on the medial aspect of the hemispheres to the region where these join the vermis, but is separated from the cerebellar hemispheres by a layer of connective tissue. This is continuous with the pia on the dorsal aspect of the hemispheres and with the connective tissue on the outer surface of the membrane. In the caudal part of the membrane a plexus chorioideus is present, but it is smaller and less branched than normal. In Case 1 the foramina of Luschka are patent, but the foramen of Magendie cannot be identified. In Case 2, in which there is severe leptomeningitis and an abscess in the right cerebellar hemisphere, none of the foramina can be found.

Discussion

The pathological changes in the brains in our two cases betray striking similarities to those found in most cases described in the literature. The chief common features have been a generalized hydrocephalus, an underdevelopment of the cerebellar vermis, particularly of its posterior parts, and anomalies in the roof of the dilated fourth ventricle, which has been covered by a thin membrane of a much larger size than the normal posterior medul-

ry velum and the tela chorioidea. But certain riations in the intensity of the changes have been ted in the cases described. Thus the degree of ncomitant alterations in the cerebellar hemis- eres as well as the anomalies in the vermis have ried. According to some reports the vermis has en entirely absent, but in some of these it can be en from the illustrations that a reduced vermis has, vertheless, been present. In spite of these and her variations there can be no doubt that all these ses represent one type of developmental distur- nce. Since little information of value can be ained from an analysis of the presumably secondary changes in other parts of the brain, for example, the nuclei of the brain-stem, these changes will not be discussed. Nor is analysis of the clinical features of importance.

Several attempts have been made to explain the developmental disturbances which produce this type of malformation. In recent years most authors have regarded atresia of the foramina in the roof of the fourth ventricle as the primary defect (Dandy and Blackfan, 1914; Taggart and Walker, 1942; Walker, 1944; Coleman and Troland, 1948; Maloney, 1954; Gibson, 1955, and others). This atresia is assumed to give rise to a hydrocephalus which in turn is responsible for the anomalous development of the vermis. However, for reasons which will be given below, it is here concluded that a retardation or failure of development of these foramina is not an essential factor in the production of the anomalies.

The extensive studies of Larsell (see Jansen and Brodal, 1954, 1958) have shown that in all mammals the cerebellum develops principally in the same way. The cell material destined to form the cerebellum migrates from the lateral margin of the rhombencephalon along the two cerebellar commissures which both pass in the thin cerebellar plate, the caudal part of which is continuous with what later becomes the roof of the fourth ventricle. Dow (1940) suggested that the defective development of the vermis in his dogs and in other similar cases might be due to some (unknown) factor which had prevented completion of the cerebellar commissures. This factor might well be a hydrocephalus arising at an early foetal stage (Brodal and others, 1944; Brodal, 1945) since this would produce an extension of the cerebellar plate and impede the cellular migration. Conceivably this might easily be followed by aberrations and distortions in the pattern of the medial parts of the cerebellum and, in more advanced stages, also of the hemispheres. In agreement with this hypothesis in all cases reported the vermis of the anterior lobe has been less affected than that of the posterior lobe, since the migration towards the midline begins rostrally and is completed latest caudally (see, for example, Hochstetter's Figs. 103 to 107). A failure of the foramina of Magendie and Luschka to develop might in this way be assumed to be the primary cause of the pathological changes.

That another explanation is far more likely appears, however, when a comparison is made with the findings in a strain of hydrocephalic mice with defective development of the cerebellar vermis (Brodal and others, 1944). In these mice, as in the human cases, the vermis of the anterior lobe was always less affected than the posterior vermis, and the posterior part of the fourth ventricle was covered by a membrane, consisting on its inner side of ependyma, on its outer side of connective tissue continuous with the pia. The membrane was attached to the brain-stem along the normal lines of attachment of the roof of the fourth ventricle.

Of the mice belonging to this strain only a certain number develop the anomalies under discussion which are due to a monohybrid recessive gene (Bonnevie, 1943)[1]. In a study of the development of the anomaly in foetal mice (Bonnevie and Brodal, 1946) various stages could be analysed. In embryos younger than the beginning of the eleventh day, no anomalies have ever been seen (Bonnevie, 1944). However, on the twelfth day a striking difference between normal and abnormal embryos appears. This difference concerns the area membranacea anterior of Weed (1917), which is a transitory transparent oval region in the roof of the fourth ventricle immediately caudal to the cerebellar *Anlage*. It is covered by extremely flattened ependymal cells and situated closely beneath the epidermis. Caudal to the area anterior the choroid plexus develops, the first signs of its development being seen on the eleventh day in normal embryos. In the course of the following two days the area anterior normally disappears and becomes incorporated into the plexus. At the same time an area membranacea posterior appears caudal to the developing choroid plexus, marking the beginning of the future " foramen " of Magendie[2]. In the abnormal mouse embryos, however, the area anterior is not incorporated into the plexus but persists. It is even enlarged and can be seen to bulge outwards, apparently on account of an increased intraventricular pressure. The whole roof of the fourth ventricle is extended, the median part of the choroid plexus is displaced caudally, separated from the cerebellum by the persisting area anterior, and the cerebellar plate is also changed. Its median thin part is thinner and broader than normal. During the following days the attenuation of the

[1]It is interesting in this connexion that two of Benda's (1954) cases were sisters.

[2]In the mouse embryos the "foramina" of Magendie and Luschka on all stages appear as continuous, though very thin membranes.

cerebellar plate continues. It affects chiefly its median part and is most marked caudally. The formation of the normal vermis is disturbed to a varying extent according to the degree of distension of the roof of the fourth ventricle. The findings thus confirm the hypothesis mentioned above (for particulars see Bonnevie and Brodal, 1946).

With reference to the findings in human cases it is important that in the abnormal mouse brains the hydrocephalic dilation of the ventricles sets in before any " foramina " of Luschka and Magendie are formed and at a stage of development where the median part of the cerebellar plate is still thin, particularly in its caudal third where it has a thickness of a few cell layers only. In man, according to the extensive investigations of Hochstetter (1929), the foramen of Luschka appears at a foetal stage of 195 mm. crown-rump. The appearance of the foramen of Magendie could not be definitely established, but in an embryo of 125 mm. crown-rump Hochstetter found it not developed. Although the term " area membranacea anterior " (Weed) is not used by Hochstetter (1929), this area is described and clearly seen in his illustrations, and, just as in the mice, is gradually reduced in size (see, for example, his Figs. 113, 114, 121, 146, 210 to 215). At a stage of 68 mm. crown-rump it can still be recognized (Hochstetter's Fig. 215, Pl. 31), but at the 100 mm. stage it has disappeared, and the choroid plexus is found immediately caudal to the nodulus (Hochstetter's Figs. 216 to 219, Pl. 31). The normal development in this region in man thus appears to be in all essentials similar to that in the mouse. With regard to the question concerning us here, the time of fusion of the paired *Anlages* of the cerebellum is of importance. According to Hochstetter (1929), this fusion occurs at the stage of 40 to 45 mm. crown-rump. The last part of the cerebellar plate to fuse is the nodulus, which lags considerably behind and at a stage of 120 mm. crown-rump is still a paired structure (Larsell, 1947).

From these data it is seen that in man the fusion of the two cerebellar *Anlages* is completed far in advance of the appearance of the foramina of the fourth ventricle. A pathological dilatation of the fourth ventricle, occurring as a consequence of a failure of development of the foramina, would therefore scarcely produce marked changes in the cerebellar vermis, which, by the time of the formation of the foramina, shows all its principal subdivisions (see Jansen and Brodal, 1958). If a pathological dilatation occurs at an earlier stage, however, namely when the "area membranacea anterior" still persists, *i.e.*, before approximately the 100 mm. crown-rump stage, it would probably have a profound effect on the development of the vermis. The splitting of the vermis in two more or less symmetrical halves which has been observed (Brodal, 1945) corresponds to the findings made in the mice and indicates that the distension of the roof has occurred at a very early stage. The fact that the nodulus in some cases (Sahs, 1941; Gibson, 1955), as in our own, or even the nodulus and uvula (Brodal, 1945), is represented by cerebellar tissue covering the rostral part of the membrane (see Fig. 7) also points to a disturbance occurring before the formation of the nodulus is completed. Another finding of relevance is the caudal position and rudimentary development of the median part of the choroid plexus of the fourth ventricle in our cases. In Sahs' (1941) case and in Gibson's (1955) case 1 this part of the plexus was absent, likewise in Castrillón's (1933). While such aberrations might easily be explained by a persistence of the "area anterior", since the plexus develops caudal to this, it is difficult to see any causal relationship between this feature and the lack of development of the foramen of Magendie.

The above analysis leads us to conclude that the anomalies in the cerebellum and the roof of the fourth ventricle in human cases of the type under discussion arise at a foetal stage considerably earlier than the formation of the foramina of Magendie and Luschka, and are due to an increased intraventricular pressure, the reasons of which remain unknown[3]. The mechanisms at work appear to be essentially similar to those operating in the hydrocephalic mice. If so, the causal role of a possible atresia of the foramina of the fourth ventricle appears questionable. Certain observations may be mentioned which collectively cast doubt on the generally accepted assumption that the type of malformation under discussion is due to an atresia of the foramina of Magendie and Luschka.

It is now generally agreed that these foramina are not artefacts (Dandy, 1921; Alexander, 1931; Barr, 1948; and others), but normal brains have been found in which the foramen of Magendie (Key and Retzius, 1875) or one or both foramina of Luschka (Alexander, 1931; and others) were lacking. Apparently fluid can escape from the ventricular system to the subarachnoid space without such foramina, presumably through the thin roof of the fourth ventricle.[4] On the other hand, in our Case 1 as well as in some others (Castrillón, 1933; Gibson, 1955, Case 2) one or more of the foramina have

[3]Bonnevie (1944) has been able to trace the first signs of an anomalous development in the hydrocephalic mice to the blastocyst stage. They first become manifest in the foetal coverings.

[4]The recent studies by means of radioactive isotopes on the "circulation" of the cerebrospinal fluid make clear that this problem is far more complex than hitherto believed. Other mechanisms than passage through the roof of the fourth ventricle may well be at work in hydrocephalic brains.

been patent in spite of dilatation of the ventricles and an anomalous development of the vermis. Benda (1954) as well as Walker, according to Benda, observed cases of this malformation in which the foramina were judged to be patent, since dyes passed into the spinal subarachnoid space. Clarke and Laidlaw (1958) report a case which was diagnosed as an example of atresia of the foramina of Magendie and Luschka, in which filling of the ventricular system, including a dilated fourth ventricle, was achieved by air encephalography via the lumbar route. Such observations support the contention that atresia of the foramina of Magendie and Luschka is not the primary factor responsible for the development of the anomalies in the brain in these cases.[5]

Furthermore, it appears reasonable that atresia cannot be solely responsible for the clinical symptoms, even if it may be a contributing factor, for many of the patients suffering from so-called atresia of the foramina of Magendie and Luschka have led a fairly normal life for many years. Thus our cases were 4 and 8 years respectively, Brodal's (1945) 11 years, Maloney's (1954) 6 and 13 years, Gibson's (1955) 12 and 13 years, Coleman and Troland's (1948) Case 2, 17 years, Sahs' (1941) 16 years, Walker's (1944) 20 years, Clarke and Laidlaw's (1958) 36 years, and Castrillón's (1933) almost 60 years. In most cases the clinical disturbances have been signs of increased intracranial pressure, and occasionally symptoms have been intermittent. It seems likely that patients with this anomaly are prone, sooner or later, to encounter difficulties in the escape of cerebrospinal fluid from the ventricular system, but in most the reasons for this remain obscure. In some cases a slight "serous" meningitis might have been responsible, in others physical exertions seem to have provoked acute symptoms. It is conceivable that a meningeal infection or oedema might endanger a cerebrospinal fluid circulation which is already impaired by occluded foramina of the fourth ventricle, but no entirely satisfactory explanation can at present be given of the curious fact that patients affected with this anomaly may live for years without signs of increased intracranial pressure.

Some favourable results of operative intervention in cases like those described here have been reported (Sahs, 1941; Cohen, 1942; Walker, 1944; Coleman and Troland, 1948; Maloney, 1954). The establishment of an opening between the dilated fourth ventricle (commonly, but erroneously referred to as a "cyst") and the cisterna magna may well be of importance in relieving the symptoms due to increased intracranial pressure when these occur. It will be of practical importance, therefore, to be aware of such cases which clinically, as recently suggested by Benda (1954), may properly be referred to as presenting the Dandy-Walker syndrome. A diagnostic finding of value is the raising of the transverse sinuses, which can be recognized on a radiograph of the skull and indicates an elevation of the tentorium, although this sign may be absent, as in Coleman and Troland's (1948) cases. Additional clues are given by an enlarged head, particularly an elongated occiput (Benda, 1954). When found in patients presenting signs of rather rapidly increased intracranial pressure, such findings should arouse suspicion, and a ventriculograph, or in some cases even an air encephalograph via the lumbar route, will clinch the diagnosis.

[5]Benda (1954) also has recently opposed the view of the causal role of the atresia of the foramina of Magendie and Luschka in this type of hydrocephalus, but is inclined to consider the anomalies as belonging to the group of rachischisis malformations.

Summary

The clinical and pathological anatomical findings in two cases of the "Dandy-Walker" syndrome are described. The patients were two girls, aged 4 and 7¾ years, respectively, who had presented signs of increased intracranial pressure for relatively short periods before they succumbed. Ventriculography showed a generalized hydrocephalus, with a large air-filled space in the posterior cranial fossa, indicating a cerebellar defect.

The chief anatomical findings, apart from a generalized hydrocephalus, were the following: The posterior part of the cerebellar vermis was underdeveloped, and was continuous caudally with a membrane consisting of ependyma and connective tissue which represents the extremely enlarged roof of the fourth ventricle. In Case 1, the foramina of Luschka were patent. The median part of the choroid plexus of the fourth ventricle was underdeveloped and displaced caudally.

A comparison with the findings made in adult and foetal brains belonging to a strain of mice affected with a similar type of malformation (Brodal and others, 1944; Bonnevie and Brodal, 1946) and a consideration of data from the normal development of the human brain make clear that the anomalies in the human cases originate at a stage before the foramina of Luschka and Magendie develop. This, as well as other data, for example, the occurrence of the anomalies and symptoms in cases with patent foramina, show that the atresia of the foramina found in many cases cannot be an essential factor in the production of the anatomical (and clinical) disturbances in cases of this type.

References

Alexander, L. (1931). *Z. Anat. Entwl. Gesch.*, **95**, 531.
Barr, M. L. (1948). *Brain*, **71**, 281.
Benda, C. E. (1954). *J. Neuropath. exp. Neurol.*, **13**, 14.
Bertrand, I., Medynski, C., and Salles, P. (1936). *Rev. neurol.*, **66**, 716.
Bonnevie, K. (1943). *Skr. Norske Vid. Akad. I. Math.-Naturv. Kl.* No. 4.
—— (1944). *Ibid.*, No. 10.
——, and Brodal, A. (1946). *Ibid.*, No. 4.
Brodal, A. (1945). *Ibid.*, No. 3.
——, Bonnevie, K., and Harkmark, W. (1944). *Ibid.*, No. 8.
Castrillón H. A. (1933). *Z. ges. Neurol.*, **144**, 113.
Clarke, E., and Laidlaw, J. (1958). *Neurology*, **8**, 382.
Cohen, I. (1942). *J. Mt Sinai Hosp.*, **8**, 441. Cited from Gibson, J. B. (1955).
Coleman, C. C., and Troland, C. E. (1948). *J. Neurosurg.*, **5**, 84.
Dandy, W. E. (1921). *Surg. Gynec. Obstet.*, **32**, 112.
——, and Blackfan, K. D. (1914). *Amer. J. Dis. Child.*, **8**, 406.
Dow, R. S. (1940). *J. comp. Neurol.*, **72**, 569.
Fusari, R. (1891-92). *Mem. Accad. Sci. Inst. Bologna*, Ser. 5, **2**, 643. Cited from Vogt, H., and Astwazaturow, M. (1912), and Gibson, J. B. (1955).
Gibson, J. B. (1955). *J. Neuropath. exp. Neurol.*, **14**, 244.
Hochstetter, F. (1929). *Beiträge zur Entwicklungsgeschichte des menschlichen Gehirns*, vol. II. Deuticke, Vienna and Leipzig.
Jansen, J., and Brodal, A. (1954). *Aspects of Cerebellar Anatomy*. Johan Grundt Tanum, Oslo.
——, —— (1958). *Das Kleinhirn*. In W. von Möllendorff's *Handbuch der mikroskopischen Anatomie des Menschen* (band 4, teil 8). Springer-Verlag, Berlin, Göttingen, Heidelberg
Key, A., and Retzius, G. (1875). *Studien in der Anatomie des Nervensystems und des Bindegewebes*. 1st half. Samson & Wallin, Stockholm.
Larsell, O. (1947). *J. comp. Neurol.*, **87**, 85.
Lesbre and Forgeot (1905). *Rev. gén. Méd. vét.*, **6**, 198. Cited from Bertrand, I., Medynski, Ch., and Salles, P. (1936).
Lyssenkow, N. K. (1931). *Virchows Arch. path. Anat.*, **280**, 61.
Maloney, A. F. J. (1954). *J. Neurol. Neurosurg. Psychiat.*, **17**, 134.
Pines, L., and Surabaschwili, A. (1932). *Arch. Psychiat. Nervenkr.*, **96**, 718.
Rossi, U. (1891). *Sperimentale* (Mem.), **45**, 518. Cited from Sahs, A. L. (1941).
—— (1892). *Ibid.*, **46**, 310. Cited from Sahs, A. L. (1941).
Sahs, A. L. (1941). *Arch. Path. (Chicago)*, **32**, 52.
Scarff, I. E. (1933). *J. nerv. ment. Dis.*, **78**, 400. Cited from Gibson, J. B. (1955).
Schwarzkopf, H. (1950). *Arch. Psychiat. Nervenkr.*, **185**, 84.
Shryock, E. H., and Alexander, H. B. (1943). *Bull. Los Angeles neurol. Soc.*, **8**, 11. Cited from Coleman, C. C., and Troland, C. E. (1948).
Sidenberg, S. S., Kessler, M. M., and Wolpaw, R. (1946). *J. Pediat.*, **28**, 719.
Taggart, J. K., and Walker, A. E. (1942). *Arch. Neurol. Psychiat. (Chicago)*, **48**, 583.
Verhaart, W. J. C. (1942). *J. comp. Neurol.*, **77**, 49.
Vogt, H., and Astwazaturow, M. (1912). *Arch. Psychiat. Nervenkr.*, **49**, 75.
Walker, A. E. (1944). *J. Neuropath. exp. Neurol.*, **3**, 368.
Weed, L. H. (1917). *Carneg. Inst. Publ. No. 225. Contr. to Embr.*, **5**, No. 14.
Woskressenski, S. (1911). *Z. ges. Neurol. Psychiat. (Orig.)*, **6**, 38.

. Neurol. Neurosurg. Psychiat., 1959, 22, 109.

A METHOD FOR THE LOCALIZATION AND PRODUCTION OF DISCRETE DESTRUCTIVE LESIONS IN BRAIN

BY

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That the more distressing symptoms of Parkinsonism and other hyperkinetic disorders may be relieved surgically has now gained general acceptance. At the present time procedures in which destructive lesions, localized by a stereotactic method and made through a small cranial opening, have gained almost universal preference. It is proposed to describe such a technique. It has been found to work well in practice, disturbance to the patient is minimal, electro-physiological studies are facilitated since general anaesthesia is unnecessary, and the stereotactic instrument used is relatively inexpensive.

Stereotaxis

In practice, since most workers in the field of human stereotaxy use part of the visualized ventricular system as a reference point in localization (Hankinson and Amador, 1956), the problem is reduced to the insertion of a cannula or electrode through the skull in the direction of an identical point plotted on two radiographs taken in planes at right angles to each other. The depth of insertion must also be known.

It has been found that a high degree of accuracy is obtainable by the use of a direction indicator so constructed that an adjustment in one plane can be made without altering the position in that at right angles to it.

Description of Instrument

The instrument (Fig. 1), made of stainless steel, consists of a ball drilled centrally and fitted to an electrode or cannula carrier (a). Into this carrier a directing rod (b) can be inserted. Two lead-containing markers (c) are fitted to the rod in such a way that the distance between

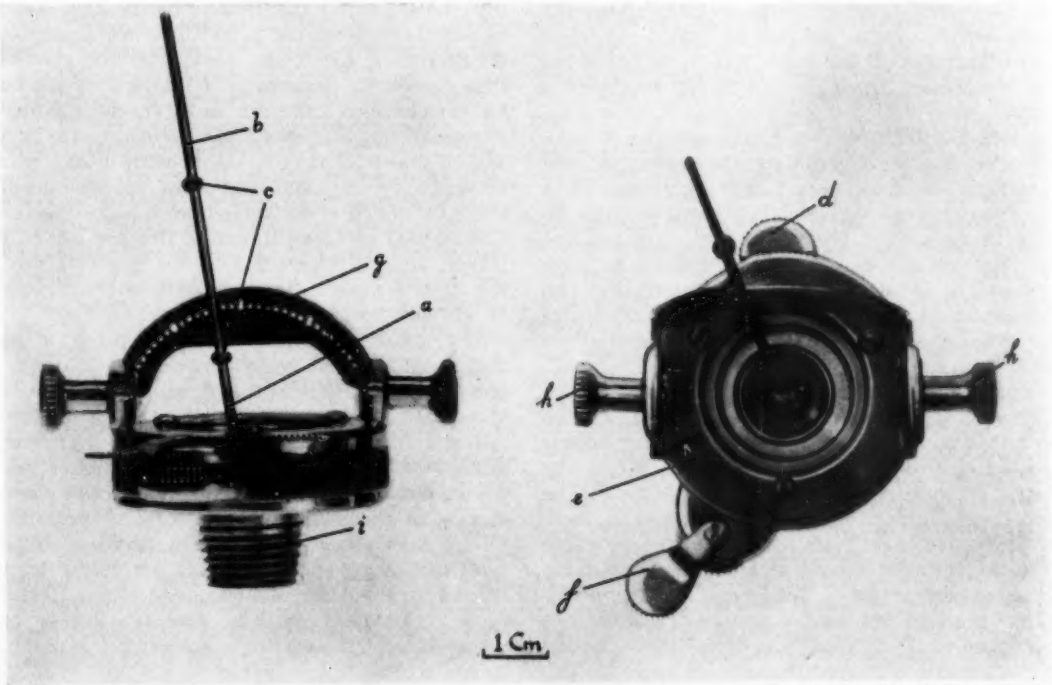

FIG. 1.—Stereotactic instrument.

them is equal to that from the lower one to the centre of rotation of the ball. The ball may be locked in any desired position by means of the lever (d) and the mechanism is so designed that this action does not result in slight movement of the ball and carrier. A turntable (e) can be turned into any position, but when lever (f) is moved in a clockwise direction to the "on" position a "click" mechanism comes into play so that rotation through an angle of precisely 90° may be appreciated by touch alone. On the turntable a curved perforated scale (g) is mounted in such a way that it can be made to touch the directing rod. The centre of the circles formed by the arcs of the scale itself and the curved guides in which it runs is at the centre of rotation of the ball. The scale can be locked in any position by thumb screws (h). A lead strip is inserted between steel outer layers in the construction of the scale. Rigid fixation to the skull is obtained by the tapered tubular mounting (i) which has a screw thread and which fits the hole made by a 17 mm. Hudson burr. The ball is situated in the lower part of the mounting.

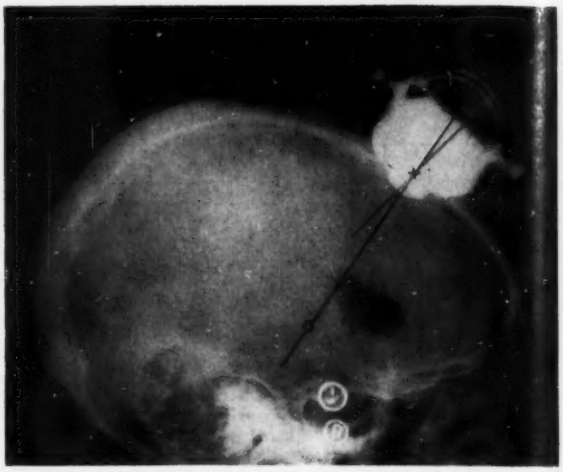

FIG. 2.—Line drawn from target through centre of rotation indicating correct position on scale.

Method of Localization

The conventional radiographic centring points are best discarded in favour of the nasion-inion line and one at right angles to it passing through two symmetrically placed points on the line 3 cm. in front of the external auditory meatus. Radio-opaque markers are fixed to the scalp at all four points and a further marker is used to indicate the site of proposed insertion of the stereotactic instrument. The selection of this point is a matter of preference and has no bearing on the method of localization. When either the globus pallidus or thalamus has been the target a point about 4 cm. from the mid-line near the coronal suture has been used.

All radiographic studies are made with a constant object-film and tube-film distance (F.F.D.). A skull stand of Schönander or Barazzetti type is an advantage but not a necessity. A F.F.D. of 90 cm. or more is preferable.

Air is introduced into the ventricular system. Antero-posterior and lateral radiographs are taken and the target marked on each film. Superimposition of a brow-down and brow-up lateral projection may be necessary to define the position of the target if the posterior end of the third ventricle is required as a reference point. That the target marked on the two films represents an identical point within the skull may be checked since the vertical height of each point above the nasion-inion line should be the same.

The whole procedure is carried out under local anaesthesia and with the patient supine. Through a 3 cm. incision at the point already determined, a burr hole is made in the skull using a 17 mm. Hudson burr. The stereotactic instrument is then screwed home. The turntable is rotated until a "click" position is reached, the lever (f) moved to the "off" setting and the turntable again rotated until the curved perforated scale is lying parallel to the sagittal plane. The lever (f) is then moved to the "on" position and remains so throughout the rest of the procedure. The "click" device will now operate whenever the scale is moved through an angle of 90°. The directing rod is next inserted into the carrier. The ball is freed by means of lever (d) and, aided by reference to the two films on which the target is marked, an attempt to estimate the correct line by eye is made. The ball is then locked and the curved scale is moved against the directing rod and a radiograph taken. The scale is then moved clear of the rod, rotated through an angle of 90°, placed in contact with the rod again, and a further radiograph taken in this plane. The films are then developed, fixed, and rapidly dried. If rinsed in 90% alcohol and then put between blotting paper they are ready in two minutes. A fine pencilled line is drawn on each film extending the line of the directing rod towards the cranial cavity. The distance on the films between the two markers on the rod is measured and a point of equal distance from the lower marker on the pencilled line then represents the centre of rotation of the ball. A further pencilled line from the target through the centre of rotation and extended outwards to cross the perforated scale is drawn. The point on the scale in each projection at which the directing rod must be positioned to be correctly aimed at the target can now be seen (Fig. 2). Care should be taken to ensure that the curved scale is locked in a position touching the directing rod before the latter is moved so that movement in only one plane at a time is possible.

The above procedure will only result in accurate alignment when the angle of correction necessary in the plane at right angles to that being corrected is less than about 10°. At angles greater than this the error due to radiographic distortion may become significant, the critical point depending on variations in F.F.D. (A communication discussing this and other theoretical aspects of the method is in course of preparation by Dr. J. A. V. Bates.) The error, however, is never so great that by the above method a position within the 10° margin will not be attained. At worst, therefore, a further two films may be necessary before accurate positioning of the carrier is achieved. In practice it is usual to obtain a satisfactory position after the first

FIG. 3.—Calculation of depth.

two radiographs have been taken provided a reasonably careful alignment is made when initially positioning the directing rod.

Calculation of Depth

The distance from the upper end of the electrode or cannula carrier to the target, measured on a radiograph, represents the required depth modified not only by radiographic magnification but also by foreshortening due to angulation in the plane at right angles to that being examined. The actual depth is best calculated by insertion of a cannula of known length and this when measured on the radiograph enables the magnification factor to be determined. Greater accuracy is obtained by using a short-length of cannula near to the central *x*-ray beam (Bates, personal communication).

Since experience has shown that as far as the globus pallidus and thalamus are concerned, the actual depth is always more than 8 cm., a cannula 8 cm. long with a small hole drilled through it at right angles to its axis 2 cm. from the distal end is inserted to its full extent into the carrier. The hole in the cannula can be seen radiographically and the distance on the film which represents an actual length of 2 cm. measured (Fig. 3). If x represents the true distance from the end of the 8 cm. cannula to the target, a the length of the 2 cm. segment when measured on the radiograph, and b the distance from the end of the cannula to the target measured on the film, $x=\frac{2b}{a}$. This therefore represents the value in centimetres which must be added to the 8 cm. insertion in order that the tip of the cannula may coincide with the target.

Making the Lesion

The making of a focal coagulative lesion with diathermy current was initially tried but the technique was felt to be unreliable and was abandoned. A method of chemical coagulation (Cooper, 1955) using absolute alcohol had been described and this substance, coloured with dye, was injected into necropsy material. It was found that the fluid tended to take the line of least resistance running in the direction of main fibre tracts. About this time a further communication by the same author (Cooper, 1956) indicated that he was now increasing the viscosity of the injected fluid by the addition of ethocel. This mixture too was subjected to the same examination but again, in necropsy material at least, the degree of spread was found to be unpredictable. Further studies seemed to indicate that the chemical agent injected should be in the form of a thick paste. Kaolin powder was therefore added to the alcohol-ethocel solution ("etopalin") and it is this mixture which has been used during the past two years. No adverse effects have been attributed to its use. Since no patient has died, it remains to be established what part each constituent of the mixture plays in the making of a lesion which on clinical grounds appears to be satisfactory.

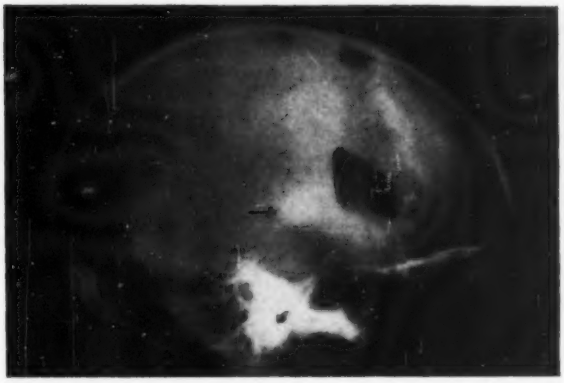

FIG. 4.—Post-operative film, showing outline of injected "alcohol paste".

A cannula with a stop at the required distance is inserted into the instrument carrier. A No. 18 gauge spinal puncture needle with the bevelled point removed will be found to be satisfactory. One millilitre "hypaque" and 3 ml. "etopalin" are mixed together and kaolin powder sterilized by dry heat is added until a thick paste of the consistency of toothpaste (dentifrice) is obtained. The paste is inserted into the open barrel of a 20 ml. syringe, the plunger inserted, and the mixture injected into the open barrel of a narrow bore 1 ml. syringe. The type used for tuberculin testing will be found to meet all requirements. If the paste is made correctly it is not possible to fill the narrow bore syringe by drawing back the plunger in the usual manner. The syringe is attached to the cannula and the plunger depressed very slowly, the effect on tremor and muscle tone being constantly assessed. A second syringe must be used if more than 1 ml. of the material is required. In thalamic procedures a total of about 1 ml. is usually necessary (Fig. 4); for the globus pallidus slightly more. The paste sets hard at room temperature but is readily soluble in acetone.

Recurrence of significant tremor and rigidity is rare and a second injection at a later date is hardly ever necessary.

Summary

A small, relatively light and inexpensive stereotactic instrument is described. An account of its use and the making of a localized destructive lesion in brain by the injection of "alcohol paste" is presented.

I am indebted to Messrs. K. O. Ford, the makers of the stereotactic instrument, for their most helpful cooperation during its development.

I am also indebted to Dr. A. K. Pittman, of Ciba Laboratories, for his help in making "etopalin" solution available.

References

Bates, J. A. V. Personal communication.
Cooper, I. S. (1955). *Science*, **121**, 217.
—— (1956). *The Neurosurgical Alleviation of Parkinsonism.* Charles C. Thomas, Springfield, Illinois.
Hankinson, J. and Amador, L. V. (1956). *Postgrad. med. J.*, 32, 28.

THE FEBRUARY (1959) ISSUE

The February (1959) issue contains the following papers:—

A Clinical and Radiological Correlation of the Lesions Produced by Chemopallidectomy and Thalamectomy. Gonzalo J. Bravo and Irving S. Cooper

Some Aspects of the Effects of Acute Reserpine Treatment on Behaviour. Peter H. Glow

Physiological Tremor in Children. John Marshall

The Mechanism of the Pain in Trigeminal Neuralgia. Eric Kugelberg and Ulf Lindblom

Lumbosacral Spina Bifida Cystica with Craniovertebral Anomalies: Report of Two Cases Presenting with Neurological Disorder in Adult Life. John D. Spillane and Lambert Rogers

The Relief of Myotonia by the Use of a Potassium-binding Resin. Victor Tompkins, R. G. Lascelles, and Brian McKinney

The Estimation of Motility During Rest or Sleep. G. H. Cox and E. Marley

Blood Cerebrospinal Fluid Bromide Ratios in Mental Patients. A. J. Coppen

An Angiographic Test of Collateral Circulation through the Anterior Segment of the Circle of Willis. C. B. Sedzimir

The Application in General Medical Conditions of a Visual Method of Assessing and Representing Generalized Electro-encephalographic Abnormalities. John Laidlaw

Proceedings of the Society of British Neurological Surgeons: 58th Meeting

Book Reviews

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s.* 6*d.*

J. Neurol. Neurosurg. Psychiat., 1959, 22, 113.

THE EFFECTS OF INDUCED HYPERTHERMIA ON PATIENTS WITH MULTIPLE SCLEROSIS*

BY

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Several authors have reported that induced hyperthermia causes new neurological signs to develop in patients with multiple sclerosis. Collins (1938) observed that a patient with multiple sclerosis while receiving fever therapy developed a series of neurological signs that reversed when the fever therapy was terminated. Simons (1937) pointed out that 62% of patients with multiple sclerosis gave a history of becoming weak when exposed to heat. Guthrie (1951) found that neurological signs can develop in a patient with multiple sclerosis when only a leg or arm is immersed in hot water, and he pointed out the frequent diminution in visual acuity and the appearance of scotomata when patients are totally or partially immersed in hot water.

In an earlier study (Nelson, Jeffreys, and McDowell, 1958), we investigated the effects of induced hyperthermia by hot baths not only on patients with multiple sclerosis but on patients with a variety of other diseases of the nervous system. It was found that each of the 12 patients with multiple sclerosis developed neurological changes and that these were usually multiple (an average of 2·8 per patient). It was also found, however, that 55% of patients with diseases other than multiple sclerosis developed neurological changes. These were usually single signs and tended to occur at higher elevations of body temperature than in patients with multiple sclerosis. Patients with multiple sclerosis frequently developed alterations in extraocular movements, including the appearance of nystagmus, signs of dysfunction of the medial longitudinal fasciculus, and paralysis of extraocular muscles. Visual acuity also frequently decreased. It was found that three patients with multiple sclerosis developed signs before any elevation of body temperature was recorded. Because of the possibility that this may have been due to the manner in which the test was performed (taking the oral temperature every five minutes), the present study was undertaken to study the occurrence of neurological changes in patients with multiple sclerosis with particular attention to the temperature of onset.

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Methods and Materials

Fourteen patients with a clinical diagnosis of multiple sclerosis were studied. Two of these were confined to bed and had far advanced disease; 12 were ambulant and had moderately advanced disease. There were eight women and six men in the study. Their average age was 42 years with a range from 29 to 57 years. The duration of the disease varied from two and a half years to 28 years. Eight patients (57%) gave a history of intolerance to heat, usually profound weakness in a hot bath.

Their body temperatures were raised in two different ways. Five patients were heated with infra-red lamps which arched over the bed two feet from the skin and radiated the patient from the nipple line down. The patient was covered with a blanket in order to raise humidity and to reduce the cooling effects of sweat evaporation. Skin and rectal temperatures were recorded using skin and rectal thermocouples. In this manner the skin temperature was raised to between 114 and 117°F. and the rectal temperatures were raised from 1·5 to 4·7°F. in 30 to 72 minutes.

Nine patients were heated by immersing them up to the nipple line in a hot bath with the water temperature at 105°F. and then elevating the temperature of the bath to 106 to 110°F. over a 10 to 15-minute period. Body temperature was recorded utilizing a rectal thermocouple and rectal temperatures were elevated from 1 to 4°F. in 23 to 40 minutes. The thermocouple was introduced 6 in. or more into the rectum and the buttocks were taped together to prevent any water from entering the anus.

These two techniques were utilized as a means of gradually elevating the body temperatures so that careful note could be made of the body temperature at which new signs occurred. Blood pressures, visual acuity, pupillary size, dysarthria, nystagmus, range of extraocular movements, and evidence of weakness of the extremities were

recorded. A previous study (Nelson *et al.*, 1958) indicated that the most frequent neurological changes were diminished visual acuity and changes in extraocular movements, and led us to concentrate on these observations. Changes in reflexes, strength, coordination, etc., may have occurred during this study but due to their inconsistent change in the first study and difficulty in evaluating and recording them, they were not included. After discontinuing heating, the patients were examined at intervals until control levels of body temperature and neurological signs were reached. Visual acuity was measured with a Snellen chart at 15 feet in the patients who were heated with the lamps and the other patients who were heated in the bath had visual acuity measured utilizing a Lebensohn near-vision chart.

Results

Table I indicates the type of neurological signs observed and the frequency with which they appeared in these 14 patients when their body temperatures were raised from 1°F. to 4·7°F. It can be seen that diminished visual acuity and changes in extraocular movements accounted for the majority of the changes. One patient developed no measurable signs, three developed only one sign, but the others developed an average of three new signs. The patient who developed no signs had evidence of a transverse myelopathy and never had had evidence of cranial nerve dysfunction. The three patients who developed only one sign also had predominantly evidence of spinal cord involvement. One developed paraparesis, one developed horizontal nystagmus (there was an earlier history of vertigo during exacerbations), and the other patient developed loss of visual acuity. This last patient had no earlier history of loss of visual acuity and had never shown it on prior examination. This is the only patient in this or the earlier study who developed a sign of dysfunction of the nervous system without some earlier evidence or history of similar dysfunction.

TABLE I

TYPE OF NEUROLOGICAL CHANGES

Type of Sign	No. of Signs
Diminished visual acuity	9
Horizontal nystagmus*	7
Vertical nystagmus*	6
Diplopia	4
Medial longitudinal fasciculus syndrome	4
Dysarthria	3
Paraparesis	3
Upward gaze palsy	1
Rectus muscle palsy	1

*Not present at beginning of test.

There were eight patients who were in remission, the last change in neurological status dating from six months to six years before the heat study. Six patients were in an active stage of the illness at the time of the study. Table II shows a comparison between these two groups and the temperature elevation at which the first sign occurred and the number of signs which developed. These figures suggest that the patients who were in remission showed fewer signs and that the elevation of body temperature at the appearance of the first sign was higher than for those patients with evidence of activity of the disease at the time of the study.

TABLE II

RELATION OF BODY TEMPERATURE TO NUMBER AND OCCURRENCE OF SIGNS IN PATIENTS WITH ACTIVE AND INACTIVE MULTIPLE SCLEROSIS

Patient	Body Temperature Elevation at Appearance of First Sign	Total No. of Signs
Patients in Remission		
1	0·3	2
2	1·3	3
3	—	0
4	2·2	3
5	2·7	1
6	2·0	2
7	1·9	1
8	0·9	1
Patients in Exacerbation		
1	1·6	3
2	1·6	3
3	1·3	4
4	0·3	5
5	0·5	5
6	0·9	4

All patients who developed neurological changes showed an elevation of body temperature before the appearance of the first of these signs. It varied from 0·3°F. to 2·7°F. The patients who received infra-red heat showed the first sign at a mean exposure time of 42 minutes compared with a mean immersion time of 20 minutes in the other group. Neurological signs appeared at this range of temperature elevation regardless of whether the patient was heated very slowly (as with infra-red lamps) or rapidly (as in hot water).

To further investigate whether these neurological changes depend upon an elevation of body temperature or were perhaps due to the stress of the test situation, the following studies were done.

One patient (K.B.) had developed the first sign (nystagmus on lateral gaze) after 24 minutes of radiant heat when her body temperature had been raised 1·6°F. She was placed in a hot bath for two hours and 15 minutes. Her body temperature was not allowed to rise more than 1·6°F. during the period and no neurological changes occurred. When her body temperature was allowed to rise 1·7°F. at the end of this study she developed nystagmus, which disappeared when her body temperature fell again to 1·6°F. Similar results occurred in another patient who had shown his first sign in the bath after 23 minutes when his body temperature was raised by 1·3°F. This patient was studied at

later date in the warm bath, at which time his body temperature was raised 0·4°F. to 0·9°F. for one hour and 50 minutes. During this time no changes in the neurological examination occurred. A third patient was very sensitive to heat and had shown a first neurological change at 0·5°F. body temperature elevation after seven minutes of immersion in the hot bath. This was checked a second time with only the feet and legs immersed in hot water. On this examination the first sign occurred at 0·4°F. after eight minutes of immersion. In this patient, who was very sensitive to heat, changes did occur with partial immersion but not until there had been the same body temperature elevation as during the first test.

Comparison of blood pressure changes between the patients who received radiant heat and those who received heat by hot water revealed that those in the group heated by infra-red lamps showed blood pressures which remained the same or showed slight elevation, and in the other group, though the diastolic blood pressures fell significantly, there was no significant difference in the numbers of signs which developed.

Neurological signs which appeared on exposure to heat tended to revert to control levels while the body temperature was above that at which the first sign occurred. Table III compares the body temperature elevation at which the first sign occurred with the temperature at which the first sign disappeared and that at which the last sign disappeared. Twelve patients are reported, for one developed no change in signs and data on one are lacking. In nine of these 12 patients the neurological changes disappeared when body temperature was above that at which the first sign appeared. Two patients had neurological signs reversed while the body temperature was still climbing.

TABLE III

RELATIONSHIP OF APPEARANCE AND DISAPPEARANCE OF NEUROLOGICAL SIGNS TO ELEVATION OF BODY TEMPERATURE

Patient	Body Temperature at First Sign (°F.)	Body Temperature at End of Test (°F.)	Body Temperature at First Sign of Disappearance (°F.)	Body Temperature at Last Sign of Disappearance (°F.)
Immersion in Hot Water				
1	1·3	2·2	2·2	2·0
2	0·3	1·0	1·0*	1·0
3	2·2	3·8	3·8	3·3
4	2·7	2·8	2·8*	2·8
5	2·0	2·5	1·2	1·0
6	0·5	0·7	0·5	0·5
7	0·9	1·3	2·4*	2·4
8	0·9	1·7	1·7	1·4
Radiant Heat				
9	0·3	0·5	−0·3	−0·3
10	1·9	4·2	4·3*	4·3
11	1·6	2·3	1·8*	1·8
12	1·6	2·6	2·2	1·7

*All signs disappeared at the same temperature.

Discussion

Eight of the patients in this series gave a history of weakness on exposure to heat. Seven gave a history of generalized weakness in hot baths (one of these also had dysarthria) and one gave a history of weakness of the legs only. Our patients had often found it necessary to give up hot baths due to severe weakness and the inconvenience of lying helpless in the water until someone arrived to give them assistance in leaving the tub.

It appears that most patients with multiple sclerosis will develop one or more additional neurological signs when their body temperatures are raised 0·5°F. to 2·5°F. A particular temperature elevation seems necessary before signs appear, and changes apparently do not occur as a result of the stress of the test or drop in systemic blood pressure. The additional signs which appear have with one exception occurred during an active phase of the illness in the past. The signs which appear during induced hyperthermia disappear when the patient is cooled, but often when the body temperature is at a higher level than that at which the first signs appeared. This suggests that there is some type of adaptation during heating.

The aetiology of these neurological changes is obscure. It may be the heat itself which causes dysfunction in parts of the nervous system which have suffered prior damage by demyelinating plaques. Elevation of the body temperature to a certain level may also release a humoral substance which acts on nervous tissue.

Though the appearance of neurological signs upon elevation of body temperature is by no means specific for multiple sclerosis, the appearance of multiple signs when the body temperature is elevated between 0·5°F. and 2·5°F. speaks in favour of this diagnosis. These studies also indicate that signs of neurological dysfunction are more likely to occur after elevation of the body temperature when the disease process is active.

Summary and Conclusions

Eight of 14 patients with multiple sclerosis gave a history of weakness when exposed to heat or hot baths.

Thirteen of 14 patients developed neurological signs when the body temperatures were elevated 1·3 ± 0·7°F.

Ten patients developed multiple signs. Three patients developed single signs and these patients

mostly showed evidence of spinal cord damage on neurological examination.

The occurrence of neurological changes seemed to be related only to the body temperature elevation and not to length of exposure or to depression of blood pressure.

Changes most frequently found were ocular motility changes and diminution in visual acuity.

Nine patients showed a reversion to the control observations when the body temperature was above that at which the first neurological sign appeared.

The appearance of new neurological signs after raising the body temperature is more frequent when the disease is active.

References

Collins, R. T. (1938). *Bull. neurol. Inst. N.Y.*, **7**, 291.
Guthrie, T. C. (1951). *A.M.A. Arch. Neurol. Psychiat.*, **65**, 437.
Nelson, D. A., Jeffreys, W. H., and McDowell, F. (1958). *Ibid.*, **79**, 31.
Simons, D. J. (1937). *Bull. neurol. Inst. N.Y.*, **6**, 385.

J. Neurol. Neurosurg. Psychiat., 1959, 22, 117.

THE CHOLESTEROL AND CHOLESTEROL ESTER CONTENT OF CEREBROSPINAL FLUID IN PATIENTS WITH MULTIPLE SCLEROSIS AND OTHER NEUROLOGICAL DISEASES*

BY

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Cumings (1953, 1955) showed that demyelination of the human brain caused by multiple sclerosis resulted in a loss of free cholesterol and the appearance of cholesterol esters in the involved areas. Cholesterol is a principal constituent of myelin and, according to Cumings, exists in the normal brain entirely as the free non-esterified sterol. It seemed of interest to determine the cholesterol content of the cerebrospinal fluid, and the proportion of free to esterified cholesterol normally present. The possibility existed that the total concentration and state of the cholesterol was different in the cerebrospinal fluid of patients with multiple sclerosis, reflecting the changes in the brain. The cerebrospinal fluid was chosen for this study rather than the blood serum because it is in direct contact with areas of demyelination. Also, small changes in the large serum " pool " of cholesterol might be difficult to evaluate.

A procedure for the accurate determination of small amounts of cholesterol and cholesterol ester in the cerebrospinal fluid was devised. This was based upon a new method for the extraction of cholesterol developed in this laboratory (Roboz, Hess, Di Nella, and Cevallos, 1958) and a new technique for separating free and esterified cholesterol by silicic acid column chromatography (Fillerup and Mead, 1953).

The cholesterol and cholesterol ester concentrations in the cerebrospinal fluid were determined in a group of patients with a firmly established diagnosis of multiple sclerosis. These results are compared with values obtained in normal individuals and in a series of patients with various neurological disorders.

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†Portions of this paper are taken from a dissertation to be presented to the Graduate School in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Since the cerebrospinal fluid γ globulin concentration is thought to be an aid in the diagnosis of multiple sclerosis, this was determined and the results compared with the cholesterol concentration.

Materials and Methods

Cerebrospinal fluid was obtained by lumbar puncture from most of the 53 patients included in this study. In a minority of cases fluid removed during air studies was utilized. The diagnosis of each patient was established by a thorough history and neurological examination, combined with air studies and arteriography where indicated. Especially strict criteria were applied in the selection of 13 multiple sclerosis patients. A history of remission and exacerbation was present in most, and all had evidence of dissemination of lesions. The onset of the disease in all cases was before the age of 40 years.

Included in the sample of neurological diseases were eight patients with seizures. A few represented idiopathic epilepsy while most were probably symptomatic. Each had a pneumoencephalogram taken but this failed to demonstrate a neoplasm.

In addition to routine studies the γ-globulin concentration in the cerebrospinal fluid of the multiple sclerosis patients was determined by the zinc sulphate precipitation technique reported by Roboz, Hess, and Forster (1953). Values over 5 mg. per 100 ml. are considered elevated in this laboratory.

Cholesterol and cholesterol ester were extracted from 10 ml. of cerebrospinal fluid by the method of Roboz and others (1958) and determined by the chromatographic technique of Papadopoulos, Cevallos, and Hess (1958). This method utilizes a silicic acid column and the selective elution of free and ester cholesterol followed by their colorimetric estimation.

Results

Since it was desirable to perform the cholesterol analysis on 10 ml. of cerebrospinal fluid, it was difficult to survey a large number of normal individuals. The total cholesterol content in the cerebrospinal fluid of six patients diagnosed as

neurotics with no neurological disease averaged 0·33 mg. per 100 ml., ranging from 0·26 to 0·43. Of this total, 0·17 mg. (range: 0·14 to 0·20) was in the free state, and 0·16 mg. (range: 0·12 to 0·23) represented cholesterol ester. It is recognized that the number of "normal" controls is quite small; emphasis will therefore be placed on a comparison of the levels obtained in the different diagnostic groupings.

Table I presents the cholesterol content—free, esterified, and total—of the cerebrospinal fluid of 13 patients with multiple sclerosis. When the averages of these values are compared with those of the normals, it is seen that the principal difference was in the cholesterol ester fraction. An increase in cholesterol ester was chiefly responsible for the higher total cholesterol levels in the patients with multiple sclerosis.

TABLE I

CHOLESTEROL CONTENT IN CEREBROSPINAL FLUID IN MULTIPLE SCLEROSIS

Patient	γ-Globulin (mg.%)	Cholesterol			
		Free (mg.%)	Ester (mg.%)	Total (mg.%)	Percentage as Ester
1	5·6	0·35	0·27	0·62	43
2	10·5	0·16	0·30	0·46	65
3	0·8	0·21	0·24	0·45	53
4	13·0	0·26	0·50	0·76	65
5	1·1	0·23	0·45	0·68	66
6	13·1	0·20	0·21	0·41	50
7	0·8	0·18	0·49	0·67	73
8	10·6	0·18	0·21	0·40	52
9	1·7	0·23	0·22	0·45	53
10*	1·7	0·13	0·15	0·28	54
11	3·4	0·23	0·27	0·50	54
12	5·4	0·16	0·19	0·35	54
13	10·2	0·23	0·37	0·60	61
Mean	6·7	0·21	0·30	0·51	57

*Acute disseminated encephalomyelitis.

Table II lists the cerebrospinal fluid cholesterol levels in patients with a variety of neurological disorders. The free cholesterol content was found to vary more than the ester. For example, free cholesterol ranged from 0·18 to 0·35 mg. per 100 ml. in patients with a convulsive disorder, while the ester varied between 0·14 and 0·26 mg. per 100 ml. in this group. High levels of total cholesterol were found in cases of cerebral infarction (1·04, 0·96, 0·71), severe head trauma (0·68, 0·65), intracerebral haematoma (1·08), and glioblastoma multiforme (1·35). Augmented amounts of both free and esterified cholesterol appear to be responsible for these high totals.

The calculation of the percentage of the total cholesterol as ester revealed a significant difference between the multiple sclerosis patients and those with other diseases (Tables I and II). Five patients with multiple sclerosis had cholesterol ester levels

TABLE II

CHOLESTEROL CONTENT IN CEREBROSPINAL FLUID IN VARIOUS NEUROLOGICAL DISORDERS

Diagnosis	Cholesterol			Percentage as Ester	Comment
	Free (mg.%)	Ester (mg.%)	Total (mg.%)		
Convulsive disorder	0·35	0·20	0·55	36	See text
	0·21	0·25	0·47	53	
	0·19	0·35	0·44	56	
	0·22	0·20	0·42	47	
	0·25	0·14	0·39	36	
	0·22	0·23	0·45	51	
	0·21	0·26	0·47	55	
	0·18	0·23	0·41	53	
Head trauma	0·17	0·12	0·29	41	Cerebral concussion
	0·26	0·39	0·65	60	Prolonged coma
	0·30	0·21	0·52	40	Cerebral concussion
	0·37	0·31	0·68	44	Subdural haematoma
Cerebral infarction	0·45	0·59	1·04	57	Died
	0·29	0·42	0·71	59	
	0·17	0·21	0·38	55	Two months after onset
	0·24	0·31	0·55	56	
	0·21	0·23	0·48	48	
	0·21	0·21	0·42	50	
	0·44	0·52	0·96	54	Severe deficit
	0·20	0·16	0·36	44	Rapid recovery
Aneurysm	0·28	0·23	0·51	45	Clear fluid
	0·61	0·47	1·08	43	Intracerebral haematoma
Brain tumour	0·20	0·21	0·41	51	
	0·60	0·75	1·35	56	Glioblastoma
Pre-senile dementia	0·24	0·27	0·51	53	Cerebral atrophy (P.E.G.)
	0·32	0·29	0·61	47	,,
C.N.S. syphilis	0·31	0·20	0·52	38	Tabes dorsalis
	0·27	0·22	0·49	45	Paresis
Peripheral neuropathy	0·18	0·18	0·36	50	Aetiology undetermined
	0·26	0·14	0·40	35	,,
	0·29	0·31	0·60	52	Bell's palsy
Osteo-arthritis of cervical spine	0·17	0·16	0·33	48	Root compression
	0·37	0·18	0·55	33	Long tract signs
Subacute combined degeneration (pernicious anaemia)	0·25	0·22	0·47	47	Severe cord changes

which were in excess of 60% of the total cholesterol. Of the 40 patients bearing other diagnoses (including the six normals), none had more than 60% of the total cholesterol as ester, and only one had a level of 60%.

The percentage of ester also correlated best with the degree of functional deficit possessed by individual patients with multiple sclerosis. The patients numbered 2, 4, 5, and 13 in Table I had the most severe involvement clinically; these patients all had raised percentages of cholesterol ester. However,

patient number 7 had the largest amount of cholesterol in the ester form, yet had a mild illness, with retrobulbar neuritis as the chief manifestation. Conversely, the eighth patient, although severely disabled by a disseminated disease, had relatively low cholesterol and cholesterol ester values in the cerebrospinal fluid. Examinations of the cerebrospinal fluid in this case during the one week after an exacerbation revealed almost identical levels.

The γ-globulin concentration was elevated in seven of the patients with multiple sclerosis. The γ-globulin and percentage of cholesterol as ester were both increased in three patients. Abnormalities of one or the other of these two determinations were present in nine of the 13 cases.

Although this report is not primarily concerned with serum cholesterol levels, the relationship between serum and cerebrospinal fluid cholesterol content is of interest. A patient with myxoedema had a serum cholesterol level of 406 mg. per 100 ml. (normal: 50 to 250), and a cerebrospinal fluid level of 0·55 mg. per 100 ml. Two other patients with serum levels of 288 and 256 mg. per 100 ml. had cerebrospinal fluid values of 0·57 and 0·50 respectively.

Discussion

Plaut and Rudy (1933) investigated the cholesterol content of the cerebrospinal fluid in neurological diseases but did not determine the cholesterol ester fraction. They reported a normal level varying from 0·06 to 0·22 mg. per 100 ml., although they indicated that cholesterol may be absent from normal cerebrospinal fluid. They found an increase of cholesterol in patients with cerebral arteriosclerosis, dementia paralytica, brain tumour, brain abscess, and other diseases. Patients with multiple sclerosis were evidently not studied. It is significant that Plaut and Rudy found a lower level of total cholesterol in their controls than we did. The method of determination employed by these investigators was less sensitive than the modern methods utilized in this study, a fact which was emphasized by their occasional failure to find cholesterol in the cerebrospinal fluid samples. The separation and determination of very small quantities of cholesterol and cholesterol ester has only recently been made practicable by the application of column chromatography.

It is not surprising that destruction of brain or spinal cord tissue by various disease processes was accompanied by an increased cholesterol content of the cerebrospinal fluid. The human brain, and especially the white matter, is rich in cholesterol which may be released into the cerebrospinal fluid. Both this study, and the work of Plaut and Rudy, indicate that increased serum cholesterol levels do not influence the cerebrospinal fluid concentration in patients without neurological disease.

Increased levels of both free and esterified cholesterol were found in the cerebrospinal fluid of patients with cerebral infarction, brain tumour, and head trauma, as well as in multiple sclerosis. The multiple sclerosis group was separated from the other diagnostic categories by the presence in several cases of a cholesterol ester fraction which constituted over 60% of the total cholesterol. This finding correlates well with the observations of Cumings (1955). The decrease in free cholesterol and the appearance of cholesterol ester in demyelinated areas of the brains of patients with multiple sclerosis, reported by this worker, is thus reflected by an augmented proportion of cholesterol as ester in the cerebrospinal fluid. The data are insufficient to establish a correlation betwen the cerebrospinal fluid results and the activity of demyelination: more patients must be studied. An extension of this series is also desirable since the low γ-globulin levels of several of the multiple sclerosis patients are contrary to previous experience in this laboratory and may indicate that this group was not fully representative of the disease. If further studies now in progress confirm this report, the determination of the percentage of esterified cholesterol in the cerebrospinal fluid may well be a valuable aid to the diagnosis of multiple sclerosis.

Summary

The cholesterol and cholesterol ester content of the cerebrospinal fluid was determined in six normal individuals, 13 patients with multiple sclerosis, and 34 patients with other neurological diseases. While levels of free and esterified cholesterol were raised in the cerebrospinal fluid of patients with a variety of neurological diseases, only multiple sclerosis patients were characterized by a proportion of ester which was over 60% of the total cholesterol. This finding correlates well with previous investigations of demyelinated tissue by Cumings. It is concluded that the determination of the percentage of esterified cholesterol in the cerebrospinal fluid is a promising adjunct in the diagnosis of multiple sclerosis.

References

Cumings, J. N. (1953). *Brain*, **76**, 551.
—— (1955). *Ibid.*, **78**, 554.
Fillerup, D. L., and Mead, J. F. (1953). *Proc. Soc. exp. Biol. (N.Y.)*, **83**, 574.
Papadopoulos, N., Cevallos, W. and Hess, W. C. (1958). *J. Neurochem.* In press.
Plaut, F., and Rudy, H. (1933). *Z. ges. Neurol. Psychiat.*, **146**, 229.
Roboz, E., Hess, W. C., and Forster, F. M. (1953). *Neurology*, **3**, 410.
Roboz, E., Hess, W. C., Di Nella, R. R., and Cevallos, W. (1958). *J. Lab. clin. Med.*, **52**, 158.

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ACUTE DEMYELINATING DISEASE COMPLICATING HERPES ZOSTER

BY

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Judging by the literature on the subject of the central nervous complications of herpes zoster, demyelination seems rare as a sequel. Up till 1945 Gordon and Tucker could find no recorded case in the few necropsy reports on encephalitis or myelitis complicating this infection. Nor have we been able to trace any proven case in the recent literature. This seems all the more remarkable since an early stage of a perivenous demyelinating encephalomyelitis is by no means a rare complication of varicella (Miller, Stanton, and Gibbons, 1956).

In the following two cases there were clinical grounds for believing that a demyelinating type of reaction was present.

Case Reports

Case 1.—T. Sano, a woman, aged 25, was admitted to the Third Department of Internal Medicine, Tokyo University, on March 16, 1956, under the care of Professor S. Okinaka. The following history was obtained. In the middle of February, 1956, a widespread herpetic eruption appeared, extending from the right costal margin upwards to the neck and involving the right arm. Two weeks later she noticed urgency and frequency of micturition. On March 12 numbness was felt around the lower ribs and quickly spread upwards to the chest and arms and downwards to the abdomen and lower limbs, which by February 14 had become weak. On the next day she developed urinary and rectal incontinence. When admitted on March 16, she was dyspnoeic. The neck was slightly stiff. The cranial nerves were normal. All four limbs were markedly weak and a sensory level at C.4 was obtained. The deep reflexes were depressed whilst both plantar responses were extensor. The cerebrospinal fluid contained 26 cells per c.mm. and 40 mg. per 100 ml. of protein.

A diagnosis of acute myelitis due to the virus of herpes zoster was made. She was treated with prednisolone, A.C.T.H., and acromycin. After 10 days, power had returned to the limbs and at the end of a further five days sensation was normal, except in the left hand. Sphincter control was regained by the end of six weeks. On May 17 she was discharged fully recovered.

First Relapse.—Early in December, 1956, she complained of giddiness, vomiting, and numbness of the left hand. The symptoms passed off after a few days but returned again on December 19 with hiccough. Prednisolone was given without effect. Three days before readmission on December 19 double incontinence recurred.

Examination showed hyperaemia of the optic discs, well marked lateral nystagmus, hyperaesthesia, and weakness of the left upper limb, bilateral cerebellar ataxia, and exaggeration of all deep reflexes, left more than right.

The diagnosis now seemed to lie between disseminated encephalomyelitis and multiple sclerosis. The response to prednisolone, 10 mg. daily, was satisfactory. By December 25 incontinence had cleared up and other symptoms had improved. By January 16, 1957, the only abnormal signs were nystagmus and sensory disturbance in the left hand. Prednisolone was discontinued.

Second Relapse.—Early in February, 1957, she again became ataxic and incontinent. Prednisolone was re-started and by the end of the month she had begun to improve. On April 14, when the drug was discontinued, all signs had cleared except nystagmus and sensory loss in the left hand.

Third Relapse.—On April 21, 1957, incontinence returned with headache and generalized itching. On April 27 knee and ankle jerks were all diminished. Prednisolone, 20 mg., was started again and within five days sphincter control had improved. The dose of prednisolone was gradually reduced, except for a few days when incontinence returned. The drug was finally stopped at the beginning of October.

Fourth Relapse.—Ten days after the discontinuation of prednisolone, incontinence returned and was accompanied by mild fever, abdominal discomfort, and neuralgic pains which spread to the chest and upper extremities with some weakness of the hands. Prednisolone was at once resumed and was continued in a dose of 7·5 mg. By the end of May, 1958, 5,457 mg. had been given.

Apart from a return of mild bladder symptoms for a

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fortnight in June, 1958, she had no relapse till December of that year. Prednisolone was discontinued on November 30, 1958.

Case 2.—R. Nakano, a high school girl, aged 14, was apparently in good health until January 15, 1958, when she noticed a rash over the right upper chest. Two days later she felt tired but on the following day went to a cinema. During the performance she saw double and by the next morning her family noticed that she squinted. She consulted an ophthalmologist who found bilateral paresis of the internal rectus muscle. During the next few days vision deteriorated in the left eye. Both hands, the abdomen, and lower limbs felt numb, the right leg became weak, and she was unsteady when walking.

She was admitted to the Neuropsychiatric Department of Kumamoto University under the care of Professor K. Miyagawa on January 24. Temperature was normal. She was drowsy but normally orientated and cooperated well in the examination. Slight neck stiffness was present but she denied headache. A crusted herpetic eruption was seen in the distribution of the right third dorsal segment. The fundi were normal, but with the left eye she could only count fingers, and the left pupil responded sluggishly to light. There was paresis of conjugate movement to the left and of both internal recti with impairment of upward movement of both eyes. Nystagmus was present to the right and vertically. The corneal reflexes were brisk and sensation was normal on the face. A slight right facial weakness of peripheral type was present. The remaining cranial nerves were normal.

In the upper limbs both hand grips were weak, left more than right, fine movements were clumsy and a marked degree of cerebellar ataxia was present on finger-nose testing. Hypaesthesia was noted in the fingers of both hands with a mild degree of postural loss and faulty two-point discrimination. Hyperpathia was present over segments C.2 and 3 and D.2 and 3 with impairment of all forms of sensation below D.4 and gross postural loss in the toes of both feet. The abdominal reflexes were absent. There was slight loss of power in both lower limbs, particularly the right. Deep reflexes were depressed in the upper but exaggerated in the lower limbs, with the exception of the right knee jerk which was depressed. Both plantar responses were extensor.

Since the clinical picture suggested an acute demyelinating process, treatment with cortisone, 25 mg. four hourly, was begun.

On January 30, the patient was more alert. Neck stiffness was less marked. Vision in the left eye showed perception of light only; right eye 0·4 (normal 1·2). There was complete paresis on conjugate movement to the left. Hand grips were both weaker, there was no voluntary movement of the right leg and early paresis in the left leg. Urine was being retained now. By January 31, vision in the right eye and power in the left leg had further deteriorated; otherwise her condition was unchanged. Cortisone was increased to 200 mg. By February 3, both pupils were dilated, and she could only count fingers with the right eye; vision in the left eye was unchanged. Paresis of the upper limbs was more marked. Postural loss in the joints of the right arm up to and including the elbow and in the left arm in the fingers and wrist joints was complete. Sensory level was now D.1 on the left side. Paraplegia was now complete except for feeble extension at the left knee. Postural loss was found in all joints in both lower limbs (hip joints not tested). Slight progression of symptoms during the previous three days was noted on February 5. The left upper limb reflexes were absent, with complete paraplegia and postural loss in the lower limbs. On February 8, prednisolone, 20 mg., was given in addition to cortisone, 150 mg.

On February 17, slight improvement was noted. Hand movements were appreciated with the left eye, and nystagmus was less marked. Both hand grips were stronger. The sensory level was now D.4. Power had slightly returned to the left knee but postural loss in both lower limbs remained complete. Cortisone was reduced to 100 mg. on February 14.

Despite the development of a sacral decubitus the patient continued to improve. By the end of March she was able to read, ocular movements had returned to normal, and nystagmus was minimal. Apart from a mild degree of residual weakness in both hand grips and faulty two-point discrimination in the fingers, the upper limbs were normal. A sensory level was no longer found on the trunk. In the lower limbs a mild spastic paraparesis, superficial sensory loss, and postural loss at the ankles and toes remained. Bladder control returned. After débridement, the sacral sore began to heal. From February 14 the dose of cortisone was progressively decreased and finally stopped on March 2. Prednisolone, 10 mg., was continued for a further four days, the total amount given being 410 mg. and of cortisone 3,725 mg.

On May 21, 1958, examination by Dr. S. Seguchi showed the following:—Vision both eyes 1·2 (normal); no nystagmus; ocular movements were full. Power, reflexes, and sensation were normal in the upper limbs, without ataxia. Slight weakness of the right lower limb persisted; knee jerks were within normal limits but the right ankle jerk was exaggerated with unsustained clonus. Both plantar responses were early extensor. Bladder control was normal. The bedsore was nearly healed. The patient could walk several hundred metres without support.

Discussion

In the first of these two cases, two weeks after an attack of herpes zoster, frequency and urgency of micturition followed by an acute myelitis naturally suggested virus as a cause. Seven months later a severe relapse raised the question of a demyelinating disease, a diagnosis later confirmed by further relapses. In this patient any attempt to decide the issue as between acute disseminated encephalomyelitis and multiple sclerosis on purely clinical grounds must take into consideration a number of facts, some relating to the case itself and others to certain aspects of the natural history of these closely related conditions.

When relapses occur in the months or years after

an attack of acute disseminated encephalomyelitis there can be three explanations (van Bogaert, 1950).

First, as a result of the original infection, the nervous system becomes sensitized and a subsequent exanthem or other type of infection may lead to a reactivation of the same lesion or may even cause a new and possibly fatal attack of encephalomyelitis. The second explanation assumes that the original illness represented the acute onset of multiple sclerosis. Lastly, in rare cases, it seems possible that multiple sclerosis may become grafted on to a previous attack of perivenous encephalomyelitis.

In our first case the latent interval of seven months before the first relapse, the clinical evidence of fresh lesions during this relapse in the form of giddiness, vomiting, and cerebellar ataxia, and lastly further relapses, seem to favour a diagnosis of multiple sclerosis, either grafted on to an attack of perivenous encephalomyelitis or arising *ab initio*. However, it is also possible that the case falls into the first of van Bogaert's categories as an example of relapsing or chronic disseminated encephalomyelitis. In addition to neck stiffness, some support for this diagnosis comes from a consideration of the response of the patient to cortisone and prednisolone. There is evidence from the literature that cortisone or A.C.T.H. may favourably influence the course of acute disseminated encephalomyelitis. For example, Miller and Gibbons (1953) observed marked improvement in eight cases so treated. On the other hand, cortisone or A.C.T.H. appear to have little effect on the course of multiple sclerosis, a conclusion first reached by Glaser and Merritt (1952) after treating 33 chronic cases.

Of more importance is the effect of this treatment in acute cases or in those which have recently relapsed. In the small series of seven cases of multiple sclerosis reported by Miller and Gibbons each had recently developed an acute episode with some objective disability. No patient who showed any evidence of spontaneous improvement was treated. They reported that the results were "profoundly disappointing", the only definite change being a decrease in spasticity and an improvement in bladder function as previously observed by Glaser and Merritt. Alajouanine, Castaigne, and Lhermitte (1956) treated 31 cases with cortisone, 21 with an oral preparation and 10 by intrathecal injection. In 11 out of 14 patients who showed improvement, the disease was of recent origin and, with one exception, there had been a recent relapse. Neither cortisone nor A.C.T.H. had any effect in a rapidly progressive case dying within six months nor in another subacute case. In none did they observe a spectacular improvement with this form of treatment and they concluded that, when it did occur, it might have been due to a spontaneous remission. Postel and Cossa (1955) reported the case of a woman aged 20, who in the course of two years had many relapses and finally became severely disabled with ocular pareses, severe ataxia, complete paraplegia, and retention of urine. At that stage cortisone was given in doses ranging from 100 to 200 mg. daily; A.C.T.H., 10 to 20 units daily, was given during quiescent periods. This régime was followed for 13 months, the patient receiving a total of 8,000 units of A.C.T.H. The authors state that cerebellar and vestibular signs cleared completely except for nystagmus, power returned to the lower limbs, the plantar responses became flexor, and she was able to lead a normal life. Treatment was maintained by means of a daily dose of 10 units of A.C.T.H. In a later paper, Cossa, Postel, Bochot, Camuzard, and Tartar (1956), improvement was reported in three out of five cases of multiple sclerosis similarly treated but they consider that this result might have occurred independently of treatment.

From these reports and a few others in the recent literature, it appears that, as a rule, neither cortisone nor A.C.T.H., when administered in the usual way, has any appreciable effect on acute episodes of multiple sclerosis. Exceptionally, however, the administration of large doses of these drugs, or of prednisolone, and their continuation in the form of a maintenance dose may be of benefit.

In Case 1 recovery from relapses coincided with the administration of prednisolone. On three occasions when the drug was withdrawn a relapse shortly followed. Finally when she was given a maintenance dose of 10 mg. daily no relapse occurred over a period of nine months.

Turning to the second case, the diagnosis might, at first glance, appear relatively straightforward, the association of bilateral blindness with an acute myelitis favouring neuromyelitis optica. This diagnosis, however, has no precise nosological status, and is used somewhat indiscriminately. On the one hand, we find cases included under this heading which, judged by the clinical and sometimes pathological evidence, are clearly examples of multiple sclerosis, whereas in a minority the same picture may be caused by acute disseminated encephalomyelitis. In the past, undue emphasis has been placed on the rarity of acute retrobulbar neuritis in this form of demyelinating disease. However, in their recent report on nine fatal cases of encephalomyelitis following preventive inoculation against rabies, Uchimura and Shiraki (1957) stress the relative frequency of visual symptoms. In two patients demyelinating lesions were found in the optic chiasm or nerves and in three others in the optic tract or at other levels of the visual pathways.

Although in distribution and form many of the demyelinated areas resembled those of multiple sclerosis, particularly in those patients who had survived some months, the authors concluded that the essential condition was one of disseminated encephalomyelitis. It seems likely that in the Japanese race, the optic nerves and chiasm are specially vulnerable in the demyelinating diseases. For example, Okinaka, Tsubaki, Kuroira, Toyokura, Imamura, and Yoshikawa (1957) state that in 270 cases of demyelinating disease reported in Japan during the past 50 years, 175 were diagnosed as probable or possible neuromyelitis optica and this diagnosis was confirmed in each of the 18 cases which came to necropsy. In only 66 cases was the diagnosis of multiple sclerosis made or suspected. Even when allowance is made for a bias towards the diagnosis of neuromyelitis optica owing to the reputed rarity of multiple sclerosis in Japan, the above ratio is impressive, being quite the reverse of that found in the western hemisphere.

From the foregoing it is clear that acute disseminated encephalomyelitis offers an alternative explanation of the clinical picture shown by our second patient, more especially in view of the presence of neck stiffness at the onset, the associated brain-stem signs, and the response to prednisolone.

Finally, if in our two patients the primary role of herpes zoster be admitted, a further reason can be added to those already given in favour of a diagnosis of acute disseminated encephalomyelitis, namely the extreme rarity with which multiple sclerosis (or neuromyelitis optica) has followed a post-exanthematous form of encephalomyelitis.

However, our attempt to reach a precise clinical diagnosis, particularly in Case 1, seems unnecessary in the light of a recent article by Ferraro (1958) on the subject of multiple sclerosis. He concludes that there are no appreciable differences, clinical or pathological, between acute multiple sclerosis and the acute and subacute varieties of post-exanthematous, post-vaccinal, and post-infectious encephalomyelitides. Furthermore, he proposes that multiple sclerosis should be labelled as the chronic variety of disseminated encephalomyelitis. "Multiple sclerosis may then represent the chronic stage of an acute disseminated encephalomyelitis and not a transformation of a disease into another one." In support of this thesis he cites *inter alia* the occurrence of abortive or monosymptomatic forms of multiple sclerosis with permanent recovery, the lack of any clinical data which allow a distinction to be made between acute disseminated encephalomyelitis and acute multiple sclerosis, and the lost importance of relapses and remissions in the diagnosis of multiple sclerosis, since these may occur in various types of disseminated encephalomyelitis. While there would be general agreement with the concept, supported by Dawson in 1916, that multiple sclerosis is basically a form of encephalomyelitis, some of the reasons put forward by Ferraro for the unification of these forms of demyelinating disease are open to criticism. For example, he tends to quote exceptional cases from the literature to prove his point, while minimizing those clinical differences that are known to exist between them, for example, the comparative rarity of relapses following the post-exanthematous and post-vaccinal types of acute disseminated encephalomyelitis compared with their commonplace occurrence in multiple sclerosis. It is true that cases are occasionally met with which tend to support his thesis (our first provides an excellent example), but these are comparatively rare. Ferraro's concept of an "infectious-allergic" or "toxic-allergic" pathogenesis of acute and chronic encephalomyelitis (multiple sclerosis), which is an elaboration of his earlier work (1944) on the allergic origin of the demyelinating diseases, is in keeping with recent thought on this subject.

However, until specific antigens or antibodies have been discovered, and the immunochemist has determined their inter-relationship in the various forms of encephalomyelitis, there seems little justification for the eclipse of multiple sclerosis as a clinical entity even though the term fails to describe the primary pathological feature of the disease.

Summary

A clinical account is given of acute demyelinating disease in two Japanese subjects, following an attack of herpes zoster. The first case was characterized by relapses and the second by the association of bilateral blindness with an acute myelitis. Both responded to prednisolone. They are discussed from the point of view of multiple sclerosis and acute disseminated encephalomyelitis.

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References

Alajouanine, T., Castaigne, P., and Lhermitte, F. (1956). *Rev. neurol.*, **94**, 352.
Bogaert, L. van (1950). *J. Neuropath. exp. Neurol.*, **9**, 219.
Cossa, P., Postel, J., Bochot, Camuzard, and Tartar (1956). *Presse méd.*, **64**, 447.
Dawson, J. W. (1916). *Edinb. med. J.*, n.s. **17**, 229.
Ferraro, A. (1944). *Arch. Neurol. Psychiat. (Chicago)*, **52**, 443.
—— (1958). *J. Neuropath. exp. Neurol.*, **17**, 278.
Gordon, I. R. S., and Tucker, M. F. (1945). *J. Neurol. Neurosurg. Psychiat.*, **8**, 40.
Glaser, G. H., and Merritt, H. H. (1952). *J. Amer. med. Ass.*, **148**, 898.
Miller, H. G., and Gibbons, J. L. (1953). *Brit. med. J.*, **2**, 1345.
——, Stanton, J. B., and Gibbons, J. L. (1956). *Quart. J. Med.*, **25**, 427.
Okinaka, S., Tsubaki, T., Kuroira, Y., Toyokura, Y., Imamura, Y., and Yoshikawa, M. (1957). *Excerpta med. (Amst.) Sect. VIII*, **10**, Congress Issue.
Postel, J., and Cossa, P. (1955). *Rev. neurol.*, **92**, 286.
Uchimura, Y., and Shiraki, H. (1957). *J. Neuropath. exp. Neurol.*, **16**, 139.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 124.

PROSOPAGNOSIA

BY

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"And what is the nature of this knowledge or recollection? I mean to ask, Whether a person, who having seen or heard or in any way perceived anything, knows not only that, but has a conception of something else which is the subject, not of the same but of some other kind of knowledge, may not be fairly said to recollect that of which he has the conception?"

"And when the recollection is derived from like things, then another consideration is sure to arise, which is, Whether the likeness in any degree falls short or not of that which is recollected?" "The Philosophy of Plato" *Phaedo* (the Jowett translation).

Does visual agnosia exist in a partial or isolated form, in which certain qualities only are affected, as opposed to generalized visual agnosia? Many workers cast doubt on this concept, maintaining that partial visual agnosia is no more than a combination of defects in vision, memory, and orientation, appearing together.

The clinical elucidation of partial visual agnosia is likely to be affected by the patient's intellectual capacity, his mental state at the time of examination, and his ability to cooperate without being influenced either by fatigue or by suggestion on the part of the examiner.

Critchley (1953), one of the leading workers in this field, states critically that "it would be dangerous to claim that a particular visual agnostic defect can occur in isolation".

There are some who consider visual agnosia as a patho-physiological optical problem derived from an organic lesion in the visual pathways, more especially the visual centres. Others maintain that visual agnosia is merely a mental disturbance which prevents the patient from evaluating properly and integrating into the general mental visual picture the various optical impressions, thus affecting the level of awareness.

Between these two extreme views is the more moderate one which holds that a physiological optical disturbance is associated with mental upset. Bay (1952, 1953) subscribes to this view, saying that visual agnosia is not in itself a specific cerebral disturbance but one where visual pathway defects are allied to mental disturbances. (Jung, 1954, who appraised Bay's book *Agnosia and Lability of Function* stated "the author wrote a book about agnosia in order to show that agnosia is a scientific phantom".) Bay described the disorders as fine defects in the visual system in the form of disturbances in sensation time, in adaptation time, in visual acuity, and in brightness discrimination.

Ettlinger (1956) rejected Bay's contentions. After analysing 30 cases of head injury, he showed that some patients had neither field nor perceptual defects, others had field but not perceptual defects, and only in eight of the 30 patients were field and perceptual defects found together. It is true that visual agnosia is frequently associated with homonymous hemianopsia, but despite this there are cases of hemianopsia without gnostic defects.

There is a special type of visual agnosia called prosopagnosia which means inability to recognize and identify known faces. The number of cases of this condition described is small. Hécaen, Angelergues, Bernhardt, and Chiarelli (1957) collected 25 cases described in the literature since 1932. In addition to the prosopagnosia, all the patients except two showed various psychosensory disturbances as well, such as unilateral agnosia of space, constructive apraxia, loss of topographical memory, alexia, acalculia, and in a few, optical disorders.

The case history that follows is unusual in that we were able to follow up the dynamic development of the symptoms of which prosopagnosia was a marked feature. In the early stages of the illness topographical disorientation, slight simultanagnosia, and achromatopsia were also found.

Case Report

A.G., a man, aged 64, was formerly a merchant, and now is a clerk. He has two grown up children. He has completed high school, speaks, reads, and writes five languages, and is right handed. He was well till five years ago, when he woke up suddenly from his sleep one night because of severe dizziness. He got out of bed and immediately fell to the floor, where he remained unconscious for some minutes. The following morning he felt completely well and carried on with his usual work. No

further details are available concerning this episode. His family did not notice any particular change in him. Two years later, when aged 61, he was again awakened at night by severe dizziness and a feeling of pressure in the head. He lost consciousness for some minutes and on recovering, suffered from headache for the next 24 hours. He felt quite well two days later and returned to work: there were no paralyses, no speech disturbance, no visual defect, and no loss of orientation.

The present illness began five days before his admission to hospital. The patient woke up with severe frontal headache which lessened somewhat during the next three hours. He had an appointment at noon of the same day and caught a bus in order to get there but on the way his headache increased and he decided to go home instead. He alighted from his bus as he had to change his route and on his way to another bus stop, on a road well known to him, he felt all of a sudden that the whole area appeared strange. He knew where he was and could not account for it. He managed to cross the road—he knew he had to do that—and boarded the correct bus in order to reach home. He paid his fare and received a ticket. The route, obviously well known to him, appeared strange and for a time he thought he had caught the wrong bus. He became anxious, gave the driver his address and asked him to see that he reached home should anything happen to him meanwhile. When he thought that he had reached his stop he alighted, but not because he recognized the surroundings, which appeared unfamiliar to him, but because he estimated that sufficient time had elapsed in order to arrive at it. He remembered these details clearly. He also remembered that while on the bus he found it difficult to distinguish men from women passengers. After getting off the bus, "I stood in the street and asked passers by how to get to my home. I gave them my address and carried on in the direction indicated." After walking for about five minutes, the approximate time needed to reach his home, he could not find it. He again turned to passers by who told him to cross the road as the required number was on the opposite side of the street. "I eventually reached home, and though I knew it was my home, it seemed strange to me." He opened the door, entered the flat which he knew was his, but the room, furniture, and pictures appeared different.

"The first thing I did was to go to the bathroom to wash. I looked in the mirror and saw a strange face. I put a cold compress on my forehead and as far as I remember, lay down for about three hours. Perhaps I slept. When I woke up I walked about the flat and noticed that the landscapes on the wall seemed covered by mist. I didn't pay any attention to the portraits."

The patient's wife was overseas at this particular time and his son lived elsewhere. He decided to go to the post office in order to telegraph his family.

"The road seemed completely strange to me though I knew it well. I asked directions from people in the street a number of times but felt I couldn't carry on. I turned back to see my doctor who lives opposite me and who has known me for years. I saw in my mind's eye the doctor's house, the steps leading to his flat, but I couldn't find it. I wandered up and down the stairs in a few houses till I saw the doctor's plate on one of the doors. A women opened the door but I didn't know who she was till I heard her say 'Come in Mr. G.'. I then realized that she was the doctor's wife. The doctor examined me and advised me to go to hospital. I remember that he measured my blood pressure and gave me a prescription. As I knew I was in Dr. A's surgery I didn't pay any attention to his face and didn't notice anything wrong in particular. It was already dark and I reached home with difficulty."

The events of the next two days are not clear. The patient said he had headaches and noticed for the first time that he did not see well with his left eye. He remembered reading the paper, but with difficulty. He understood what he read and could recall the items later.

The next day his son came to visit him. The patient did not recognize him and only realized who it was when he spoke. He returned to Dr. A. together with his son, and in his own words "I wouldn't have recognized the doctor if I hadn't known where I was going".

He was referred to an eye specialist and on the way to the latter's consulting rooms found that the streets and buildings appeared strange and unfamiliar. He remembered being examined by the eye specialist for more than half an hour, an instrument was used (apparently a perimeter), and he was asked to read. He had no difficulty in recalling these details but could not remember the doctor's face nor anything else about him that would help in describing him, such as his height, colour of hair, or facial features.

Till his admission to hospital 24 hours later he remained in the care of his son, which was a great relief to him as he was still disorientated. Though on the whole his flat still appeared unfamiliar to him the colour of the walls and the pictures on the walls partially regained their former clarity.

The drive to the hospital, along a route well known to him, appeared strange. "I knew from memory what to expect along the way—the various turnings, buildings, and landmarks, but when I passed these points they seemed different to what I had imagined."

The patient was admitted during the afternoon and was examined within a few hours. He was orientated for time and place. He complained of headache and difficulty in seeing objects, especially those to his left. In particular, he found difficulty in appreciating the facial features and expressions of people he had known for some time. The same thing was noticed in the ward. The patient was in constant contact with three doctors but for the first few days he was unable to distinguish one from the other. Later he reported that he had found a way out of the difficulty. "One is very tall, another has a moustache and wears glasses, and the third has neither glasses nor a moustache." He learnt to distinguish the doctors by their voices. "As soon as I hear your voice I know who you are and can tell you apart from your colleagues." During his first few days in hospital it took some minutes to recognize the various voices. He was

also unable to recognize the nurses. "They all looked alike" and usually he addressed them wrongly. He learnt to overcome this problem by associating a particular nurse with her duty shift. Six days after his admission he accosted a visiting doctor in his ward and spoke to him as if he were his own doctor. When asked about this later he said "but they both wear glasses".

His son visited him every day and he only recognized him when he sat down next to him and spoke, but after a few days he learnt to recognize him by his walk as well. With regard to other relations, he was able to distinguish them after some minutes of conversation. The patient reported that frequently during conversation, a face familiar to him suddenly lost its clarity.

> "If three people I know sit opposite me, after talking for a few minutes their faces very often become blurred and lose their individual characteristics and I no longer know to whom I am talking. I have to concentrate very hard in order to tell them apart and this gives me a headache."

During the early part of the patient's period in hospital he was referred back to the eye specialist who had examined him originally. The doctor remarked that he knew him as he had examined him a few days previously. The patient replied "I beg your pardon, but you are mistaken. I'm seeing you for the first time and you have never examined me before". During the examination the patient exclaimed "I am very sorry. Yes, yes, I know you now, you did examine me before because that same instrument (perimeter) is in exactly the same position on your table as it was before, the last time I was here". During this period there was no spatial disorientation. The patient knew the layout of the beds, the rooms, lavatory, dining-room, doctors' room, and hospital grounds. In walking about the grounds he could describe the various flowers he saw, could differentiate their colours, but regarding the sun and heavens, he repeated time and again that they were blurred.

Neurological Examination.—A full examination was made on August 6, 1957.

Eyes.—Left homonymous hemianopsia with macular sparing. Visual acuity 6/9 and 6/6.

Ears.—Vestibular and cochlear function normal.

Limbs.—Power, sensation, and reflexes were normal, but ataxia was detected. Abdominal reflexes were normal, and pathological reflexes were noted. Gait was normal.

Other clinical findings were: Blood pressure 160/95 mm. Hg, E.S.R. 25/50, blood picture normal. The heart showed left ventricular hypertrophy radiologically. An electrocardiogram was normal, and the lungs appeared normal.

An electroencephalogram was within normal limits.

Lumbar puncture showed cells 4/3, protein 51 mg. per 100 ml. mastix negative.

Wassermann and Kahn reactions were negative.

The basal metabolic rate was —2.

Patient's Behaviour in Hospital.—He felt well and was emotionally stable. He had normal contact with his surroundings and showed the same interest in hospital life as other patients. His only and repeated complaints were severe headaches of varying intensity and inability to recognize faces whether those of other patients or of visitors. He tried to distinguish people by other characteristics such as walk, dress, hair style, and so on. He had insight into his condition.

Psychosensory Examination.—The delivery, rate, and intonation of speech was normal. Articles shown him were named correctly and described in detail without error. Size of object or distance from the eye made no difference.

All commands were carried out correctly and without delay.

The patient read without difficulty printed and written texts both in Hebrew and Latin script. His diction and locution were satisfactory. He could tell the time and move the watch to any desired hour.

He wrote easily and correctly both in Hebrew (from right to left) and Latin (left to right) scripts. There was no difference between spontaneous writing and writing to dictation.

When asked to cross out certain letters in the script given him he did so without difficulty and without making any mistakes. In sentences where words or letters were missing, he completed the text correctly.

Calculations, both easy and hard, were performed without difficulty whether by memory or on paper. When adding, the figures were aligned correctly below one another.

Simple geometric patterns such as a square, oblong, triangle, or star were drawn properly on the blackboard.

Faces were drawn in detail but in rather primitive fashion. However, the patient admitted to never being able to draw faces well.

Animal pictures were distinguished correctly even if part of the picture was covered.

Pictures showing national costumes, scenes, maps, emblems, stamps, road signs, and so on, were correctly interpreted.

When shown pictures depicting action, for example, a policeman directing traffic, the patient was unable to indicate the meaning or intent of the picture. He saw a number of cars, recognized the policeman, mentioned a child crossing the road, but could not grasp the theme intended. When pressed, he said "something is obviously happening here but I don't know what". Similar difficulties were encountered when shown other pictures depicting action or motivation, or others with allegorical or humorous indications. As time went on his interpretation of pictures improved, but the time taken for this was not in proportion to the difficulties of the test nor were his answers given with certainty. Sometimes he was non-committal and gave more than one answer to the same problem. Four weeks after admission, picture interpretation became normal in all respects.

In the early days of his stay in hospital he went to the cinema, but left the hall after a few minutes. "I saw people but couldn't understand what was going on" he said. One month later he had no difficulties whatsoever when watching the screen.

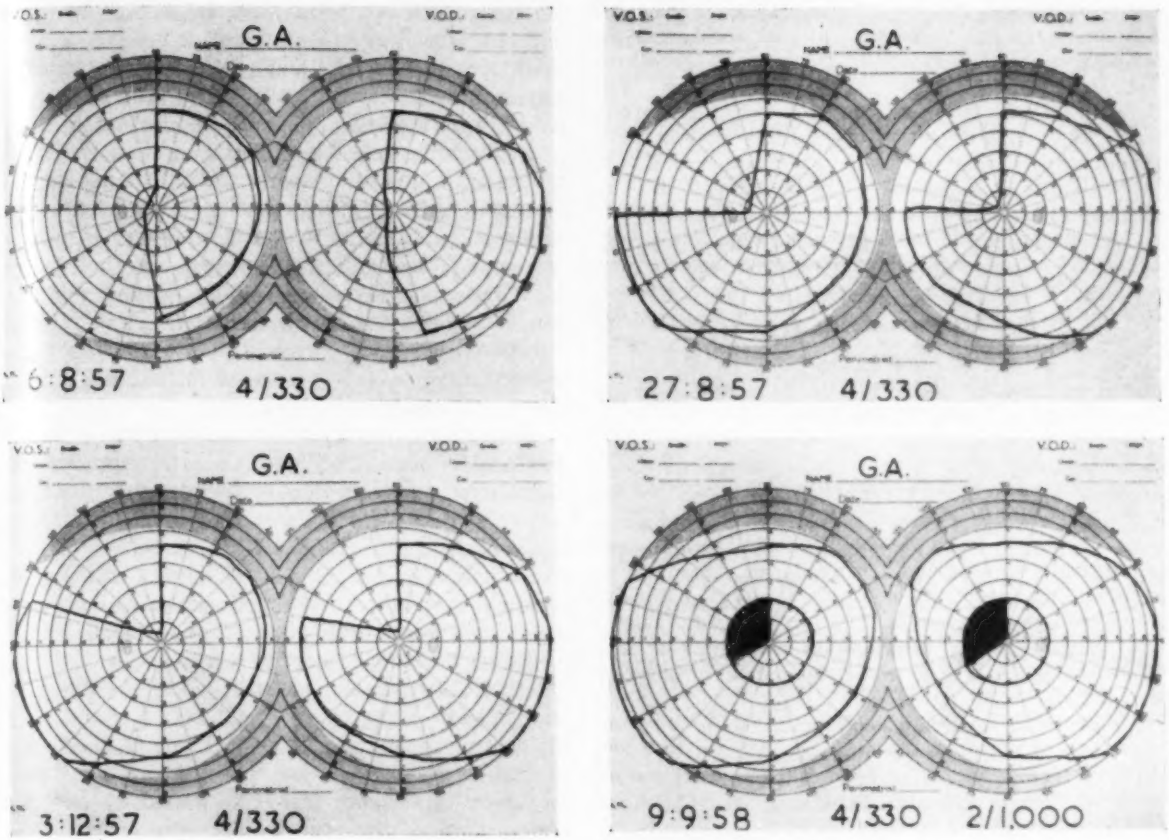

FIG. 1a to d.—Fields of vision at various dates.

No disturbances in praxis were noted at any time. The disorders in topographical memory passed off gradually within a few days of his admission to hospital. While in hospital no disturbance in colour sense was noted, but apparently it did exist before that time, for "everything I saw appeared grey and the sky always seemed cloudy. The sun looks dirty to me".

Revisualization of colours did not suffer at any time nor was there any disturbance in body schema awareness. He differentiated between right and left and between his own and other bodies. Finger gnosis was normal and there was no disturbance in time estimation.

The main defect was inability to recognize faces, whether living or from pictures. He did not recognize pictures of famous personalities that he would be expected to know such as portraits of Hitler, Stalin, Khrushchev, or Ben Gurion. If given a picture upside down he corrected the position but still was unable to say who it was. Caricatures also had no meaning for him. There was no difference whether the portrait was full face or profile. When he was shown a picture of Kosciuszko, a Polish national hero, which he could not but know, he recognized it immediately and said "every child knows this—he has such a typical cap that one can recognize him immediately".

When asked to describe certain parts of the face, such as the mouth or ears, he did so without difficulty. Revisualization of people known to him was normal; the same applied to buildings or objects which he had previously seen.

In hospital he read the paper, took an interest in daily events, and showed no objective evidence of mental deterioration.

Neurological examination 10 days after his admission showed a field defect now limited to the upper left quadrants, a normal E.E.G., and a blood pressure of 170/110 mm. Hg. The patient refused pneumoencephalography and was subsequently discharged remaining under weekly supervision in the out-patient department for the next 11 months.

According to his wife, the patient returned to his former post and carried on without encountering any particular difficulties. He travelled about alone and was completely orientated. The difficulty in recognizing faces persisted but to a lesser degree and he still found it hard at times to tell who was greeting him in the street. Three months after the onset of the illness a neighbour whom he had known for years asked him a question. He replied that he did not know her but as soon as he recognized her voice he begged her pardon and explained that he was not wearing his glasses and could not see clearly in the twilight.

An interesting episode occurred after he had left hospital, when the doctor who had treated him in the neurological ward met him in the street. The doctor walked alongside him for nearly five minutes. The patient looked at him frequently but did not recognize him. Finally the doctor asked him how he was. The patient stopped and said "Your face is so familiar" and paused. Then he continued, "I recognize you now—in hospital you don't wear a hat."

His wife stated that when they were expecting guests, he always asked beforehand who they were. Four months after the onset of the illness he still had difficulty in recognizing faces. He said, "I see people and not individuals, but as soon as they speak or make some movement I know who's who." As time passed on and with repeated examinations this difficulty in recognizing faces was the only defect found persisting.

Summary of Clinical Findings

1. In the early stages of the illness prosopagnosia was associated with topographical disorientation, simultaneous agnosia and achromatopsia, all of which passed off gradually. Six months after the onset of the illness the prosopagnosia had declined to a great extent.
2. No intellectual deterioration was noted at any time nor was any change seen in his critical faculties or memory.
3. The only neurological finding early on was homonymous hemianopia which soon shrank to a left upper quadrant defect. The last examination performed on September 9, 1958, disclosed that the hemianopic defect had shrunk still further (Fig. 1d). The boundaries of the peripheral fields are now normal. There is a dense left upper quadrantic paracentral scotoma of a type which indicates a lesion of the lower lip of the calcarine cortex.

Discussion

From a review of the literature it appears that pure prosopagnosia is rarely found as an isolated phenomenon. It is usually associated with other findings, such as object agnosia, alectic and apractic disturbances, and optic disorders. Our case resembles that described by Pallis in 1955. The latter's patient suffered from mitral stenosis and developed an embolus in the right posterior cerebral artery, which was later confirmed by vertebral arteriography. This patient showed prosopagnosia and achromatopsia. Topographical memory and facial revisualization were preserved as in our case. An additional finding was a noncongruous homonymous sector defect in the left upper quadrant and absolute scotomata in each field on both sides of the vertical meridian.

There is also some similarity to Hoff and Pötzl's patient, described in 1937, who showed prosopagnosia together with colour disturbance, and to a lesser extent object agnosia and spatial disorientation.

Klein and Stack (1953) reported on a patient who, after a vascular lesion, developed prosopagnosia with inability to interpret pictures, disturbance in topographical memory, inability to identify colours, and also had a left upper quadrantic field defect.

In the same year Alajouanine and his co-workers published a report of progressive cerebral atrophy in a man of 56, with transient left hemianopsia, who three and one half months later developed prosopagnosia (Alajouanine, Lhermitte, Sabouraud, and de Ribeaucourt (1953). The patient found it difficult to distinguish male from female faces and to estimate age by observing a face. In addition this patient was unable to recognize colours and suffered from simultanagnosia.

Between the years 1947 and 1955 Faust collected seven cases of cerebral trauma which were clinically similar to the picture of prosopagnosia described above, six of which also showed alexial disturbances (Faust, 1951, 1955).

Hécaen's two patients (1956) were operated on by Penfield in order to remove epileptogenic foci in the right parieto-occipital area. Post-operative prosopagnosia developed, together with other gnostic and practic disturbances (Hécaen, Penfield, Bertrand, and Malmo, 1956).

In other fairly similar cases reported the appreciation of prosopagnosia was difficult owing to the presence of other signs such as optic, memory, visual memory disturbances, and general intellectual deterioration. Heidenhain's (1927) cases belong to this group. One of his patients suffered from malacia of both occipital lobes following embolic imfarction could recognize neither his wife's nor his sister's face and could only differentiate them by their voices. But this patient also suffered from alexia, complete colour blindness, and paracentral scotoma in both upper field quadrants.

Jossmann's patient (1929) also showed a rich pathology. Following encephalitis this patient was unconscious for some days. On recovery she was unable to recognize faces. She was also unable to differentiate animals at rest but could do so when they moved. In addition to this prosopagnosia she also showed object agnosia, transient alexia, disturbance in perspective vision, and simultanagnosia.

Perhaps Hoff and Pötzl's case (1937) showed the most severe prosopagnosia. The patient did not recognize his own face in the mirror, suffered from severe colour disturbance, from spatial disorientation, disturbance in re-visualization, and optical reception. The pathological lesions in this case were "apoplectic" foci in both temporo-occipital lobes.

In 1947, Bodamer published three cases of prosopagnosia following traumatic lesions. It was Bodamer who introduced the term prosopagnosia.

In a detailed work he tried to explain this rare disturbance but in his cases too the prosopagnosia was superimposed on severe brain damage. In the first case, Uffz. S., a penetrating bullet caused a depressed fracture in the lower part of the left parietal bone and in the right occipital bone. The patient was blind for some weeks following the injury, and on partial recovery remained with a left upper quadrantic field defect, with metamorphopsia, object agnosia, disturbances in orientation, and simultaneous agnosia.

The second case was more severe. After a serious head injury Lt. H. A. lost consciousness. Examination later revealed left hemiparesis, reduced sensation over the left half of the body, and concentric bilateral hemianopsia. Psychosensory disturbances included a left-right orientation disorder, optical disturbances, difficulty in recognizing colours, and simultaneous agnosia. Concentration was also affected.

The third case, O. Geffr. B., had a fracture in the left occipital bone with severe brain damage. He showed signs of metamorphopsia, parts of pictures were blurred and distorted, and right hemianopsia and dyslexia were also found.

These three cases form the basis on which Bodamer tried to build his thesis. According to this author, prosopagnosia represents a severe regression in the gnostic sphere affecting the old and deep levels of perception. He states that the infant recognizes facial expression before recognizing the object. This is opposed to the view that maintains that the infant recognizes the object first. Recognition of the object is associated with high level optico-gnostic function. Bodamer sees in facial recognition an *Urphenomenon*, and, according to Monokaw's theory, a time recorded memory, *Chronogene Engramirung*. Following Kaila who examined the effects of faces on children's behaviour, he is of the opinion that the area around the eyes is the part which engages the infant's attention first. Bodamer calls this eye area the "ocula". In cases of prosopagnosia he thinks that the patient's attention is concentrated on these parts and cannot be withdrawn.

Bodamer's patient, H.A., said "apart from the eyes, the rest of the face is blurred. I don't see the facial characteristics of living people. The most obvious thing to me is the eye". Bodamer's theory, which is basically similar to Pötzl's, is unacceptable as it stands despite its originality and phylogenetic approach. All his cases suffered severe brain injury which probably affected brain function as a whole, and because of this detailed analysis is extremely difficult. We paid special attention to this point when examining our patient, who was able to define every part of the face whether living or from a photograph. As he improved his facial recognition became more prompt, and at no time did we consider visual function to be disturbed.

Bodamer's basic tenet that facial recognition is associated with the *Urphenomenon* is also open to criticism. It seems clear that the developing infant recognizes the mother's face as an object and not as an expression because first optical impressions are directed towards the woman's face attending him, holding him, or suckling him. At the same time the rest of the woman's body is not in the infant's field of vision and the direct facial stimuli will crowd out any lesser peripheral ones.

Recognition of facial expression depends on a number of stimuli, visual, auditory, and tactile. The child learns from experience; in the early stages he is attracted by toys which have no particular shape but which are prettily coloured or produce tones. At a later stage he plays with dolls or animals, and still later the faces of these dolls or animals take on a meaning.

As opposed to the inability to recognize facial expressions whether living or still life, our patient's ability to revisualize a face he had known previously was intact. He was also able to recall facial changes of people he knew with the passage of years. The same facility applied to places, and in common with Pallis' patient, he said, "In my mind's eye I know exactly where places are, what they look like and the squares and streets which surround them." Our patient did not show any signs of Charcot-Wilbrand's syndrome.

In seeking for yet another explanation, Goldstein's theory is also unsatisfactory, that any defined lesion in the brain creates a "disturbance of integrity" or general disturbance of behaviour. There was no personality disturbance in our patient nor did his behaviour change after his illness began. During the nine months he remained under observation no change in his character was noted. There were no signs of catastrophic reaction, of perseveration, nor of a depressive reaction (anosdiaphoria) to his illness (Critchley, 1957).

The patient did not try to suppress knowledge of his illness. There were none of the characteristic signs described by Goldstein such as inability to distinguish between figure and background. The opposite is true: he tried everything in order to overcome his disabilities. Only one specific quality suffered and that was the expression which appeared separated from the object.

In 1949, Faust suggested the term pseudo-agnosia to explain the cause of prosopagnosia together with lowering of mental activity and mild visual disturbances. Here apparently the visual stimuli suffered, but again pseudo-agnosia does not apply in our case, where intellectual function particularly was

unaffected. It is difficult to consider prosopagnosia as a sign of *Funktionswandel*. It is not easy to accept reduction or lability of visual function lasting for such a long time without other aspects of perception being affected.

There is no doubt that the degree of attention varies in patients with gnostic disturbances, due to various factors, mostly affective ones. Attention may become extremely limited. But despite this one cannot look upon these perceptual variations as explanations for prosopagnosia itself.

In the early stages of our patient's illness he was unable to grasp the meaning or intent of a picture though he could describe and evaluate each individual aspect of it clearly. This lack of interpretation could not be ascribed to lack of attention or fatigue. There are also no grounds for supposing that there was visual or mental fixation on a particular part of the picture. Similar to his inability to see pictures "alive" was his inability to obtain a living or vital impression of faces of people with whom he came into contact. The ability to elucidate the individuality of what he saw was affected.

It may be supposed that at a certain stage of his illness facial features were identical to him and he could not differentiate between male and female ones. The faces looked like similar objects to him and had no special characteristics. He lost the ability to penetrate into and feel the hidden trait of a face. This, in our opinion, is not connected with the optic or perceptual sphere, and there was no memory defect. The ability to analyse and synthesize facial pecularities, the active and creative process related to recognition, was disturbed.

Dementia is not a likely cause of prosopagnosia, simultanagnosia, or similar disorders.

The question is, To what extent a right parieto-occipital lesion by itself may explain the prosopagnosia? It may be seen from the history that our patient was stricken twice some years ago by short attacks of loss of consciousness, probably caused by small thrombotic processes, which do not leave any recognizable sequelae. The last sudden cerebral insult caused a left hemianopsia together with psychosensory disturbances of the highest degree.

Any attempt to connect these signs with the patient's premorbid personality will be valueless.

Though the patient disclosed unasked, during the early part of his illness, that he did not see colours clearly, we were unable to detect this objectively at any time. This subjective disturbance had already disappeared by the time the hemianopic field defect became quadrantic. Probably the right occipital lobe was damaged, and it is more likely that this dysfunction is closer to achromatopsia than to agnosia for colours.

At the onset of the illness topographical memory was disturbed to an acute degree. The disturbance passed off within five or six days, but while it lasted, though the patient's pictorial memory for topography was retained, he was unable to activate these stored memories when needed or when faced with the immediate problem of which way to turn. It was as if optical impressions were unable to activate the memory, or, put another way, as if orientation activity were upset. Sense of time was not at all affected and our patient used time sense in order to cancel out other deficiencies.

Some patients of this type suffer from a change in dream content. Our patient did not dream at all.

Regarding localization, our patient does not offer much more than other publications about patients of this type. One can say generally that a lesion in the parieto-occipital area of the brain, on the right more often than on the left, may cause a disturbance in the ability to recognize facial features. In the 25 cases collected by Hécaen between 1932 and 1957, the lesion was found on the right in 18, on the left in one, and no clear localization was established in three. As in most of the cases, our patient showed a left field defect affecting mainly the upper quadrants. There was no disturbance in speech, reading, or writing.

All the above facts lead us to suppose that the non-dominant hemisphere is mainly responsible for the development of prosopagnosia. Despite the fact that all the signs observed over the course of 16 months point towards a right-sided occipito-parietal lesion, it is highly likely that the two previous cerebral attacks caused bilateral damage to the brain. This opinion is supported by Dr. Ritchie Russell (personal communication) who states, "I should doubt myself whether this condition ever occurs in a lesion affecting one side of the brain only, as otherwise it would occur much more commonly than it does."

It appears that the occipito-parietal region, in addition to powers of integration and synthesis, is endowed with special creative functions. Possibly, when the latter functions are disturbed, high level qualities such as recognition of faces and meanings and expressions are affected.

Summary

A patient is presented who showed prosopagnosia, simultanagnosia, topographic disorientation, and achromatopsia. All these signs, excepting the first one, disappeared entirely after a short time. The

prosopagnosia persisted to a lesser degree over the course of a year during which time the patient remained under observation. At no time was mental deterioration noted. The only neurological finding apart from the above was a left upper quandrantic visual field defect. The literature pertaining to prosopagnosia is reviewed and theories are put forward to explain the phenomenon, which is related to dysfunction of the right occipito-parietal lobe.

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References

Alajouanine, T., Lhermitte, F., Sabouraud, O., and de Ribeaucourt, (1953). *Rev. neurol.*, **89**, 158.
Bay, E. (1952). *Dsch. Z. Nervenheilk*, **168**, 1.
—— (1953). *Brain*, **76**, 515.
Bodamer, J. (1947). *Arch. Psychiat. Nervenkr.*, **179**, 6.
Critchley, M. (1953). *The Parietal Lobes*. Arnold, London.
—— (1957). *Encephale*, **46**, 540.
Ettlinger, G. (1956). *J. Neurosurg. Psychiat.*, **19**, 297.
Faust, C. (1951). *Nervenarzt.*, **22**, 176.
— (1955). *Die zerebralen Herdstörungen bei Hinterhauptsverletzungen und ihre Beurteilung*. Thieme, Stuttgart.
Hécaen, H., Angelergues, R., Bernhardt, C., and Chiarelli, J. (1957). *Rev. neurol.*, **96**, 125.
——, Penfield, W., Bertrand, W., and Malmo, R. (1956). *A.M.A. Arch. Neurol. Psychiat.*, **75**, 400.
Heidenhain, A. (1927). *Mschr. Psychiat. Neurol.*, **66**, 61.
Hoff, H., and Pötzl, O. (1937). *Z. ges. Neurol. Psychiat.*, **159**, 367.
Jossmann, P. (1929). *Mschr. Psychiat. Neurol.*, **72**, 81.
Jung, R. (1954). *Nervenarzt*, **25**, 172.
Klein, R., and Stack, J. J. (1953). *J. ment. Sci.*, **99**, 749.
Pallis, C. A. (1955). *J. Neurol. Neurosurg. Psychiat.*, **18**, 218.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 132.

THE VALUE OF LEUCOTOMY IN RELATION TO DIAGNOSIS

BY

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In an earlier paper (Robin, 1958) the results of leucotomy were assessed by comparing a treatment group of leucotomized patients and a control group, matched for sex, age on admission, and length of admission. Apart from noting the similarity in the distribution of diagnosis in the two groups, no cognizance was taken of diagnosis when the operation was assessed. In this paper the case material has been extracted in relation to diagnosis only. For example, all cases of schizophrenia have been taken out of the series and then divided into two groups, (1) patients treated with leucotomy and (2) non-leucotomized subjects. The groups were not then composed of matched pairs or of equal numbers. They are nevertheless shown to be comparable in other respects than diagnosis alone.

Schizophrenia

Ninety-one cases of schizophrenia were found to have been treated by leucotomy and 97 cases were not so treated. The findings are set out in Table I. These two groups were comparable in their sex and age distributions and in their periods of stay in hospital to their operation dates. (Each non-leucotomized patient retained the "operation date" originally allocated to him or her.) The results in the two groups, when discharge from Runwell alone is considered, suggest that leucotomy offers at least some initial advantage. While the distribution of the tables as a whole is not quite significant at the 0·05 level, the single line concerning discharge does show a statistically significant difference favouring leucotomy. The favourable discharge rate, however, is temporary. The number of readmissions to Runwell and other hospitals is greater in the leucotomy group, and by the time of the final survey (December 31, 1955), the number of discharged patients is comparable in the two groups. The total period spent in Runwell and in all mental hospitals after operation date shows no difference between the treated and untreated groups. Fig. 1 shows the similarity in the results on the two groups one to 10 years after operation date.

Patients discharged and not readmitted to any mental hospital (under the same name) are those already designated "recovered" and are dealt with in more detail. The work and symptom status of the two groups is not dissimilar. The age distribution,

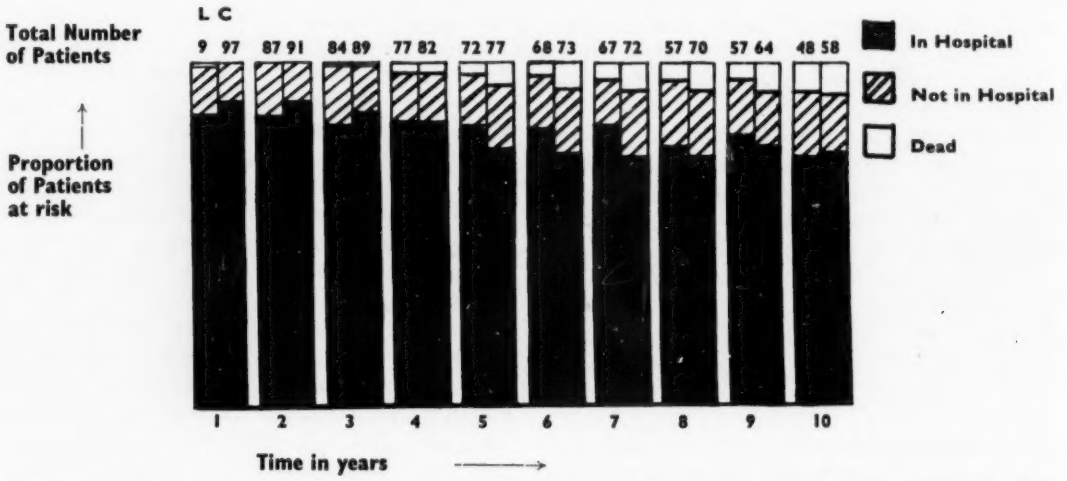

FIG. 1.—Ninety-one cases of schizophrenia subjected to leucotomy compared with 91 controls suffering from schizophrenia one to 10 years after operation.

TABLE I

RESULTS IN SCHIZOPHRENIA

	Leucotomies	Controls
Sex Distribution		
Male	20	24
Female	71	73
Total	91	97
Age of Admission		
−20	8	4
−30	44	41
−40	28	35
−50	9	14
−60	2	3
+60	0	0
*Length of Admission to Operation Date**		
− 1 mth.	8	3
− 3 mth.	2	2
− 6 mth.	3 (33)	6 (32)
− 1 yr.	7	9
− 2 yr.	13	12
− 3 yr.	10	10
− 4 yr.	7	6
− 5 yr.	5 (58)	7 (65)
−10 yr.	31	36
+10 yr.	5	6
(n = 1, X^2 = 0·14, P = 0·7)		
End-result		
Never discharged*	53 (59%)	72 (74%)
Discharged at some time	33 (37%)	20 (20%)†
Transferred	5	5
(n = 2, X^2 = 5·738, P = > 0·05)		
*Died in hospital on first admission	4	7
†(n = 1, X^2 = 4·4, P = < 0·05)		
Discharge		
Discharged at some time	33	20
Since readmitted to Runwell Hospital	13	6
Never readmitted to Runwell Hospital	20 (22%)	14 (14%)
Readmitted to other hospitals (excluding transfers)	6	4
Not readmitted to mental hospital since discharge	14 (15%)	10 (10%)
Period in Runwell Hospital since Operation		
− 1 mth.	5	3
− 3 mth.	5	2
− 6 mth.	3 (23)	3 (19)
− 1 yr.	4	7
− 2 yr.	6	4
− 3 yr.	5	6
− 4 yr.	6	7
− 5 yr.	6 (68)	10 (78)
−10 yr.	25	18
+10 yr.	26	37
Period in All Mental Hospitals since Operation		
− 1 mth.	2	3
− 3 mth.	2	2
− 6 mth.	2 (16)	2 (16)
− 1 yr.	5	2
− 2 yr.	5	7
− 3 yr.	4	5
− 4 yr.	6	7
− 5 yr.	7 (75)	11 (81)
−10 yr.	29	19
+10 yr.	29	39

*In the original matching (Robin, 1958) each control was allocated the operation date of its matched leucotomy subject. These dates have been adhered to here.

	Leucotomies	Controls
Period since Discharge in "Recovered" Patients		
− 1 yr.	2*	1*
− 2 yr.	1†	0
− 3 yr.	3	0
− 4 yr.	1	1
− 5 yr.	3	0
−10 yr.	3	5
+10 yr.	1	3
Total	14	10
*Still out in 1957		
†In mental after-care home		
Work Rating in "Recovered" Patients		
As competent as before illness	5	6
Coping	5	1
Idle or incompetent	3	0
Not contacted	1	3
Symptom Rating in "Recovered" Patients		
None	5	5
Better	6	2
Same	2	0
Worse	0	0
Not contacted	1	3
Age of Admission of "Recovered" Patients		
−20 yr.	3:cc*	1
−30 yr.	5uci	5uu
−40 yr.	4ci	3uc
−50 yr.	2i	1
Total	14	10
Length of Admission to Operation Date of "Recovered" Patients		
− 2 yr.	5ccii	6cuuu
+ 2 yr.	9ccciu	4
Period of Stay after Operation of "Recovered" Patients		
− 1 mth.	0	2u
− 3 mth.	1	2
− 6 mth.	2ci (7)	2uu (7)
− 1 yr.	1i	1c
− 2 yr.	3ciu	0
− 3 yr.	1c	0
− 4 yr.	0	0
− 5 yr.	1 (7)	2 (3)
−10 yr.	5cc	0
+10 yr.	0	1
*c = coping i = incompetent u = not contacted		
Work Rating of Patients during Discharge but Readmitted Later		
As competent as before illness	1	2
Coping	6	2
Idle or incompetent	12	6
Not contacted	0	0
Total	19	10
Symptom Rating Discharged but Later Readmitted		
No symptoms	1	3
Symptoms better	6	0
Symptoms same	8	7
Symptoms worse	4	0
Not contacted	0	0

TABLE II
RESULTS IN AFFECTIVE DISORDERS

	Leucotomies	Controls
Sex Distribution		
Male	11	6
Female	41	42
Total	52	48
(n = 1, X^2 = 1, P = 0.3)		
Age on Admission		
−20yr.	0	0
−30 yr.	2	7
−40 yr.	11	12
−50 yr.	11	9
−60 yr.	20	15
+60 yr.	8	5
Length of Admission to Operation Date		
− 1 mth.	18	15
− 3 mth.	4	6
− 6 mth.	2 (31)	5 (33)
− 1 yr.	3	1
− 2 yr.	4	6
− 3 yr.	6	8
− 4 yr.	5	3
− 5 yr.	1 (21)	1 (15)
−10 yr.	7	2
+10 yr.	2	1
(n = 1, X^2 = 1·06, P = 0·3)		
Diagnostic Sub-groups		
Melancholia	39	30
Mania	9	5
Manic-depressive psychosis	4	13
(n = 2, X^2 = 5·2, P = > 0·05)		
End-result		
Total	52	48
Never discharged*	21 (13)	14 (10)
	(7)	(2)
	(1)	(2)
Discharged at some time†	26	34
Transferred	5 (4)	0
	(1)	
	(0)	
*Died during first admission	8 (7)	4 (4)
	(1)	(0)
	(0)	(0)
†Died on subsequent admission	1 (1)	3 (1) one
	(0)	(0) died in
	(0)	(2) 1956
Total dead	9	7
Discharge		
Total discharged at some time	26	34
Discharged but subsequently readmitted	10	17
Never readmitted to Runwell Hospital	16 (15)	17 (13)
	(1)	(2)
	(0)	(2)
Readmitted to other hospitals excluding transfers	1	2
Committed suicide after first discharge		1
Total not readmitted to mental hospital since discharge	15	14
Period since Discharge of "Recovered" Patients		
− 1 yr.	0	0
− 2 yr.	0	0
− 3 yr.	0	0
− 4 yr.	1	1
− 5 yr.	1	1
− 6 yr.	2	0
− 7 yr.	3	1
− 8 yr.	1	1
− 9 yr.	2	2
−10 yr.	1	1
+10 yr.	4	7
Total	15	14
Work Rating		
As competent as before illness	6	5
Coping	9	1
Idle or incompetent	0	0
Not contacted	0	8

	Leucotomies	Controls
Symptom Rating		
None	6	6
Better	8	0
Same	1	0
Worse	0	0
Not contacted	0	8
Age on Admission of "Recovered" Patients		
−30 yr.	0	3u
−40 yr.	3cc*	3u
−50 yr.	4c	1u
−60 yr.	6cccc	7cuuuuu
+60 yr.	2cc	0
Total	15	14
Length of admission to Operation of "Recovered" Patients		
− 1 mth.	8ccccc	5uuuu
− 3 mth.	1c	3uu
− 6 mth.	0 (9)	1 (11)
− 1 yr.	0	1
− 2 yr.	0	1
− 3 yr.	2c	2uu
− 4 yr.	2c	1c
− 5 yr.	1c (6)	0 (3)
−10 yr.	1	0
+10 yr.	0	0
Period of Stay after Operation of "Recovered" Patients		
− 1 mth.	3c	4uuu
− 3 mth.	4ccc	4uuu
− 6 mth.	1c (12)	0 (12)
− 1 yr.	2c	1
− 2 yr.	2cc	3uuu
− 3 yr.	1	1
− 4 yr.	0	0
− 5 yr.	0 (3)	0 (2)
−10 yr.	2c	1
+10 yr.	0	0
*c = coping i = incompetent u = not contacted		
Period of Stay after Operation at Runwell Hospital		
− 1 mth.	7	5
− 3 mth.	7	5
− 6 mth.	3 (27)	3 (29)
− 1 yr.	6	6
− 2 yr.	4	10
− 3 yr.	2	2
− 4 yr.	4	5
− 5 yr.	1 (25)	1 (19)
−10 yr.	11	9
+10 yr.	7	2
Total	52 52	48 48
Period of Stay after Operation Date in Mental Hospitals		
− 1 mth	5	5
− 3 mth.	6	4
− 6 mth.	4 (26)	3 (28)
− 1 yr.	6	6
− 2 yr.	5	10
− 3 yr.	3	2
− 4 yr.	3	5
− 5 yr.	1 (26)	2 (20)
−10 yr.	11	9
+10 yr.	8	2
Work Rating of Patients during Discharge but Readmitted Later		
As competent as before illness	0	9
Coping	1	3
Idle or incompetent	10	6
Not contacted	0	1
Total	11	19
Rating of Patients during Symptom Discharge but Readmitted Later		
No symptoms	0	9
Symptoms better	1	4
Symptoms same	9	5
Symptoms worse	1	0
Not contacted	0	1

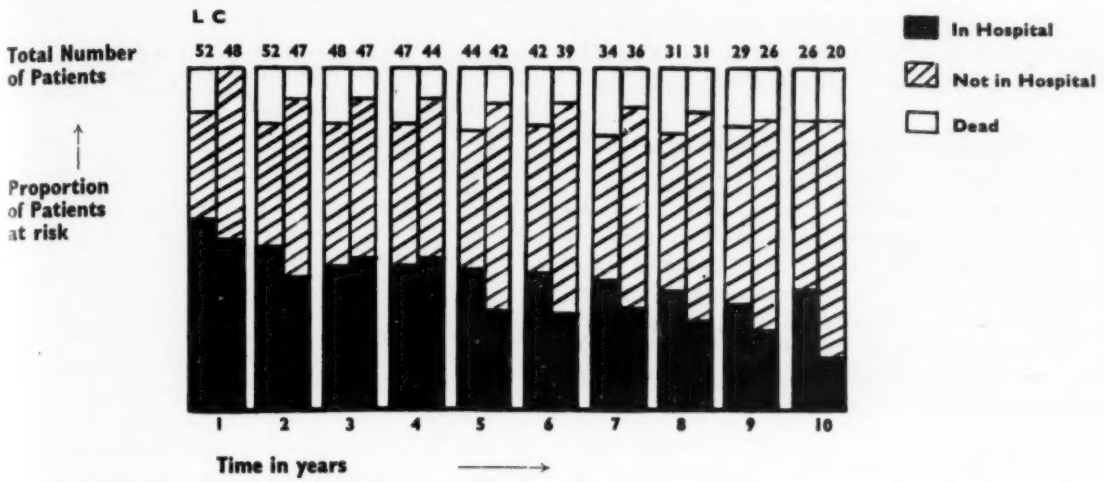
L C
Total Number of Patients
52 48 52 47 48 47 47 44 44 42 42 39 34 36 31 31 29 26 26 20
Proportion of Patients at risk
In Hospital
Not in Hospital
Dead
1 2 3 4 5 6 7 8 9 10
Time in years

FIG. 2.—Fifty-two cases of affective disorder subjected to leucotomy compared with 48 controls suffering from affective disorders one to 10 years after operation.

the period in hospital before the operation date, and the period from operation date to discharge are likewise comparable. Thus, similar patients get better in the same time.

Finally, the status of schizophrenic patients who were discharged but later readmitted to hospital is shown as far as work status and symptoms are concerned.

Affective Disorders

Fifty-two cases with affective disorders were found to have been treated by leucotomy and 48 cases were not so treated. These two groups were comparable in their sex and age distribution and in their period of stay in hospital to their operation date (Table II). (Again, each non-leucotomized patient retained the operation date originally allocated to him or her.) The distribution of diagnoses within the affective group is also shown and later results are written out so that single diagnoses—mania, melancholia, manic-depressive psychosis—may be followed. The results as far as discharge are concerned are not significantly different and are also shown in a histogram (Fig. 2).

The two "recovered" groups, leucotomy and control, have been discharged for similar periods and compare as far as can be ascertained in their work and symptom status. At least it is clearly impossible for the controls to do worse as a group than the leucotomized patients if the results in the untraced patients are made available later. The age distribution and periods in hospital before operation date are comparable in these "recovered" patients. Leucotomy does not accelerate discharge and the total period spent in Runwell and in all mental hospitals after operation date is similar. The work status of readmitted patients and their symptom status while out of hospital is shown.

Depression

Dealing with affective disorders as a cohesive group gives larger numbers and this is probably one of the reasons why this presentation is used. It can be seen, however (Table III), that the three diagnostic subgroups behave rather differently as far as outcome is concerned.

TABLE III

RESULTS IN AFFECTIVE DISORDERS REGARDLESS OF TREATMENT

	Never Discharged	Discharged never Readmitted	Discharged and Readmitted	Total
Manic depressive psychosis	3 (17·6%)	2 (11·8%)	12 (70·6%)	17
Mania	9 (64·3%)	5 (35·7%)	0 (0%)	14
Depression	23 (33·3%)	31 (44·9%)	15 (21·8%)	69

The numbers here are small but regardless of treatment manic-depressive patients (cyclothymes) are most frequently discharged and also most frequently readmitted; depressive patients almost as frequently leave hospital and the majority remain well while manic patients have a tendency to chronicity although when they do recover they do well. It is conceivable that this is an artefact which arises from psychiatrists allocating recurring cases to the manic-depressive group. On the other hand, if it is a real effect it can be seen that the distribution of these diagnoses in the affective group will affect the expected results of the group as a whole. Only in depressions, however, was a sufficient number of cases available to examine the question further.

Thirty-nine cases of depression were treated with leucotomy and 30 without the operation (Table III). The results in these cases are closely comparable.

Paraphrenia (Paranoid Psychosis)

The vast majority of this group were diagnosed as suffering from "paraphrenia" and only four cases were classified as "paranoid psychoses", two controls and two leucotomies. Twenty-two patients were treated with leucotomy and 17 were not so treated. The sex distribution, age distribution, and period of stay in hospital to operation date were comparable in the two groups (Table IV). The results likewise closely resemble each other.

TABLE IV

RESULTS IN 69 PATIENTS SUFFERING FROM DEPRESSION AND TREATED IN GROUPS KNOWN TO BE COMPARABLE FOR SEX, AGE, AND CHRONICITY

	Leucotomies	Controls
Total	39	30
Never discharged*	13	10
Discharged at any time	22	20
Transferred	4	0
Readmitted to Runwell Hospital†	7	7
Readmitted to other mental hospitals	1	3
Not readmitted since discharge	14	10
*Died on first admission	7	4
†Died on subsequent admission	1	1
Total dead	8	5

Epilepsy

Fourteen epileptics were treated with leucotomy and 13 were not so treated. Once again the results in the two groups (Table V) resemble each other closely.

Summary

The therapeutic results in cases treated by leucotomy were compared with those in patients of the same diagnosis and shown to be comparable in age, sex, and chronicity distributions, but not treated by leucotomy.

The proportion of schizophrenics discharged after the operation was greater than in the control group but the number of subsequent readmissions was also greater, so that the long-term results are comparable in the two groups.

No advantage was shown to be offered by leucotomy in affective disorders, in depression in particular, in paraphrenia, or in epilepsy, when comparisons were made with the results in similar patients not so treated. The patients who recover in the leucotomy and non-leucotomy groups appear to be comparable when sufficient numbers were available for analysis.

TABLE V

RESULTS IN PARAPHRENIA (PARANOID PSYCHOSIS)

	Leucotomies	Controls
Sex distribution		
Total in each group	22	17
Male	3	1
Female	19	16
Ages on Admission		
−30 yr.	1	0
−40 yr.	3	6
−50 yr.	13	8
−60 yr.	4	2
+60 yr.	1	1
Period from Admission to Operation Date		
− 1 mth.	1	2
− 3 mth.	3	2
− 6 mth.	0 (10)	2 (10)
− 1 yr.	0	1
− 2 yr.	6	3
− 3 yr.	6	1
− 4 yr.	1	1
− 5 yr.	2 (12)	0 (7)
−10 yr.	3	5
+10 yr.	0	0
End-results		
Never discharged (died)	14 (4)	11 (2)
Discharged at some time	7	6
Transferred	1	0
Total	22	17
Readmitted to Runwell Hospital	1	2
Readmitted to other mental hospitals	1	1
Not readmitted to hospital since discharge	5	3

TABLE VI

RESULTS IN 27 CASES DIAGNOSED AS EPILEPSY AND TREATED IN GROUPS KNOWN TO BE COMPARABLE IN AGE, SEX DISTRIBUTION, AND CHRONICITY

	Leucotomies	Controls
Never discharged	10	8
Died on same admission	1	3
Discharged at some time	3	5
Transferred	1	0
Total	15	16
Readmitted to Runwell Hospital	0	3
Died on subsequent admission	0	2
Readmitted to other mental hospitals	1	2
Not readmitted to hospital since discharge	2	0

I should like to thank Miss E. M. Brooke, statistician of the General Register Office, for statistical advice; Mlles. M. C. Fanta, A. Nicholson, D. Cobb and M. Trevallion, of the Social Service Department, Runwell Hospital, for assistance with the follow-up and, finally Dr. W. S. Maclay, Senior Medical Commissioner of the Board of Control, and his staff, Messrs. F. W. Allen and D. F. King, for information from the Board of Control's records.

REFERENCE

Robin, A. A. (1958). *J. Neurol Neurosurg. Psychiat.*, **21**, 262.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 137.

THE EFFECTS OF MEPROBAMATE AND PENTOBARBITONE SODIUM ON SLEEP AND MOTILITY DURING SLEEP: A CONTROLLED TRIAL WITH PSYCHIATRIC PATIENTS

BY

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Meprobamate (2-methyl-2-n-propyl-l, 3-propanediol dicarbamate) was synthesized by Ludwig and Piech (1951). It is an interneuronal blocking agent capable of producing muscular relaxation without affecting respiration or other vital activities (Berger, 1954). The drug produces restful sleep and generalized muscular relaxation (Borrus, 1955). It was decided to test its effect, compared with that of a placebo and pentobarbitone sodium, on motility measured on a bed providing quantified estimates of movement during sleep or recumbency.

Method

Eleven male patients aged 22 to 70 years, suffering from hyposomnia of a degree to require a night hypnotic, were studied. They slept in a ward of 10 moderately disturbed psychiatric patients. Of the 11, eight were depressed, two were schizophrenic, and one was a chronic alcoholic withdrawn from alcohol for four weeks. The trial was of the self-controlled, double-blind variety. Each patient was in the trial for 18 days, the drugs being given in random order at 9.30 p.m. For the first nine days (Series 1) the patient received on three nights each placebo alternating with meprobamate at two dose levels (400 and 800 mg.). For the second nine days (Series 2) the effect of 800 mg. meprobamate was compared with that of a conventional hypnotic (200 mg. pentobarbitone sodium) and placebo. Meprobamate and placebo were in identical tablet form and the pentobarbitone ("nembutal") in neutral-coloured capsules. The drugs were crushed and given in fluid to the patient. No additional treatment or medication was provided during the trial.

As in the method for validating the bed (Cox and Marley, 1959) the patient's motility scores were recorded hourly from the Veeder-Root counter during the period 10 p.m. to 6 a.m. by one nurse, an independent rating (as in the previous paper) of the patient's sleep being given by another. Eight patients completed a questionnaire (see previous paper) each morning relating to their night's sleep, the other three subjects being unable to comply satisfactorily on account of their mental state.

The results were dealt with by analysis of variance. A one-tail test of significance was employed if the placebo scores were to be compared with a drug score, and a two-tail test of significance if the two drug scores were to be compared.

Results

The mean and standard error of the mean scores for all results are shown in Table I.

Comparison of Effects of Placebo, Meprobamate, and Pentobarbitone Sodium on Motility.—The total motility scores between 10 p.m. and 6 a.m. for Series 1 and 2 were subjected to analysis of variance. For Series 1, the variance ratio between drugs ($F = 5{\cdot}76$, $P < 0{\cdot}01$) proving significant, the differences between mean motility scores were tested. Only 800 mg. significantly reduced movement (Table II). For Series 2, the variance ratio between drugs ($F = 4{\cdot}39$, $P < 0{\cdot}05$) was significant, so the differences between mean motility scores for the drugs were examined. Both 800 mg. meprobamate and 200 mg. pentobarbitone sodium significantly reduced movement as compared with placebo (Table II).

Time of Onset of Action of Drugs.—The mean motility scores at 11 p.m., 12 p.m., 1 a.m., and 2 a.m. were subjected to analysis of variance to ascertain the earliest moment the effect of the drug became significant. For both series this was at 12 p.m. The significant differences between the 12 p.m. mean motility scores was due in Series 1 to the effect of 800 mg. meprobamate ($t = 2{\cdot}19$, $P < 0{\cdot}02$) and in Series 2 to the significant difference between the action of placebo and 200 mg. pentobarbitone sodium ($t = 2{\cdot}6$, $P < 0{\cdot}01$). A significant effect of 800 mg. meprobamate was not evident until 1 a.m. in Series 2.

Nurses' and Patients' Ratings of Motility Scores.—There was a significant correlation in Series 1 between the nurses' ratings and the total night motility scores ($r = +0{\cdot}47$, $P < 0{\cdot}01$) but not between the patients' rating and the total motility scores ($r = +0{\cdot}22$, $P > 0{\cdot}05$). In Series 2, there was a significant correlation between both the nurses' rating and total night

TABLE I

MEAN AND STANDARD ERROR OF MEAN FOR MOTILITY SCORES, NURSES', AND PATIENTS' RATINGS DERIVED FROM PATIENTS RECEIVING PLACEBO, MEPROBAMATE, AND PENTOBARBITONE SODIUM

Scores or Ratings	No. of Patients	Indices (Units)	Series 1								
			Placebo			400 mg. Meprobamate			800 mg. Meprobamate		
			Night 1	Night 2	Night 3	Night 1	Night 2	Night 3	Night 1	Night 2	Night 3
Total motility scores (bed)	11	Mean S.E. of Mean	77·1 19·64	80·1 20·09	67·5 13·82	69·3 18·94	70·8 18·64	62·9 16·25	40·3 8·18	54·4 14·43	49·1 12·89
Nurses' total ratings	11	Mean S.E. of Mean	13·5 0·89	12·6 0·75	10·5 0·78	10·4 0·63	10·1 0·64	9·9 0·52	9·9 0·72	10·3 0·39	9·8 0·56
Patients' total ratings	8	Mean S.E. of Mean	13·6 0·98	13·8 0·25	13·6 0·55	13·8 0·83	12·5 0·66	11·8 0·75	12·0 0·69	11·1 0·97	11·5 1·09

Scores or Ratings	No. of Patients	Indices (Units)	Series 2								
			Placebo			200 mg. Pentobarbitone Sodium			800 mg. Meprobamate		
			Night 1	Night 2	Night 3	Night 1	Night 2	Night 3	Night 1	Night 2	Night 3
Total motility scores (bed)	11	Mean S.E. of Mean	65·6 12·39	62·5 14·00	67·2 12·21	29·7 8·01	42·6 7·19	44·6 8·97	40·1 9·67	63·1 11·53	48·1 8·01
Nurses' total ratings	11	Mean S.E. of Mean	11·1 0·93	10·9 0·73	11·8 0·85	9·0 0·37	9·5 0·20	9·6 0·44	9·3 0·55	10·3 0·61	9·6 0·47
Patients' total ratings	8	Mean S.E. of Mean	11·9 0·34	13·1 0·70	13·6 0·74	10·6 0·72	11·0 0·70	11·1 1·06	10·6 1·14	12·1 1·00	11·6 0·94

TABLE II

SYNOPSIS OF FINDINGS FOR DRUG TRIAL

		Series 1		Series 2	
		Placebo and 400 mg. Meprobamate	Placebo and 800 mg. Meprobamate	Placebo and 800 mg. Meprobamate	Placebo and 200 mg. Pentobarbitone Sodium
Total motility scores		$P > 0.20$ −	$P < 0.001$ +	$P < 0.05$ +	$P < 0.001$ +
Nurses' total ratings		$P < 0.001$ +	$P < 0.001$ +	$P < 0.01$ +	$P < 0.001$ +
Patients' total ratings		$P < 0.001$ +	$P < 0.001$ +	$P > 0.05$ −	$P < 0.001$ +
Patients' individual ratings	Duration of sleep	$P < 0.05$ +	$P < 0.001$ +	$P < 0.05$ +	$P < 0.001$ +
	Soundness of sleep	$P > 0.05$ −	$P < 0.01$ +	$P < 0.02$ +	$P < 0.001$ +

+ = significant difference between mean scores for placebo and drug; − = no significant difference between mean scores for placebo and drug.

motility scores ($r = +0.45$, $P<0.01$) and between the patients' rating and total motility scores ($r = +0.41$, $P < 0.01$).

Analysis of Nurses' Ratings.—As the variance ratio between drugs for Series 1 ($F = 12.95$, $P<0.001$) was significant, the mean ratings for the drugs were compared. From the nurses' ratings, it appeared that both 400 and 800 mg. meprobamate significantly reduced restlessness (Table II). For Series 2, as the variance ratio between drugs was significant ($F = 4.91$, $P < 0.05$), the mean ratings were compared. From the nurses' ratings both 800 mg. meprobamate and 200 mg. pentobarbitone sodium significantly reduced restlessness (Table II).

Analysis of Patients' Rating.—The patients' total rating for their own sleep were subjected to analysis of variance. For Series 1, as the variance ratio between drugs ($F = 12.95$, $P<0.001$) was significant, the mean ratings were tested. From the patients' ratings, both 400 and 800 mg. meprobamate significantly improved sleep (Table II). For Series 2, the variance ratio between drugs ($F = 10.16$, $P<0.001$) was significant. In this instance, 200 mg. pentobarbitone sodium but not 800 mg. meprobamate was deemed to have improved sleep significantly.

The totals for the patients' ratings were also split into the individual scores for each of the items on the questionnaire, and then subjected to analysis of variance. In Series 1, the patients stated that they slept longer both with 400 and 800 mg. meprobamate as compared with placebo (question 2 on the questionnaire) and that sleep was sounder (question 3) with the 800 mg. does as compared with placebo

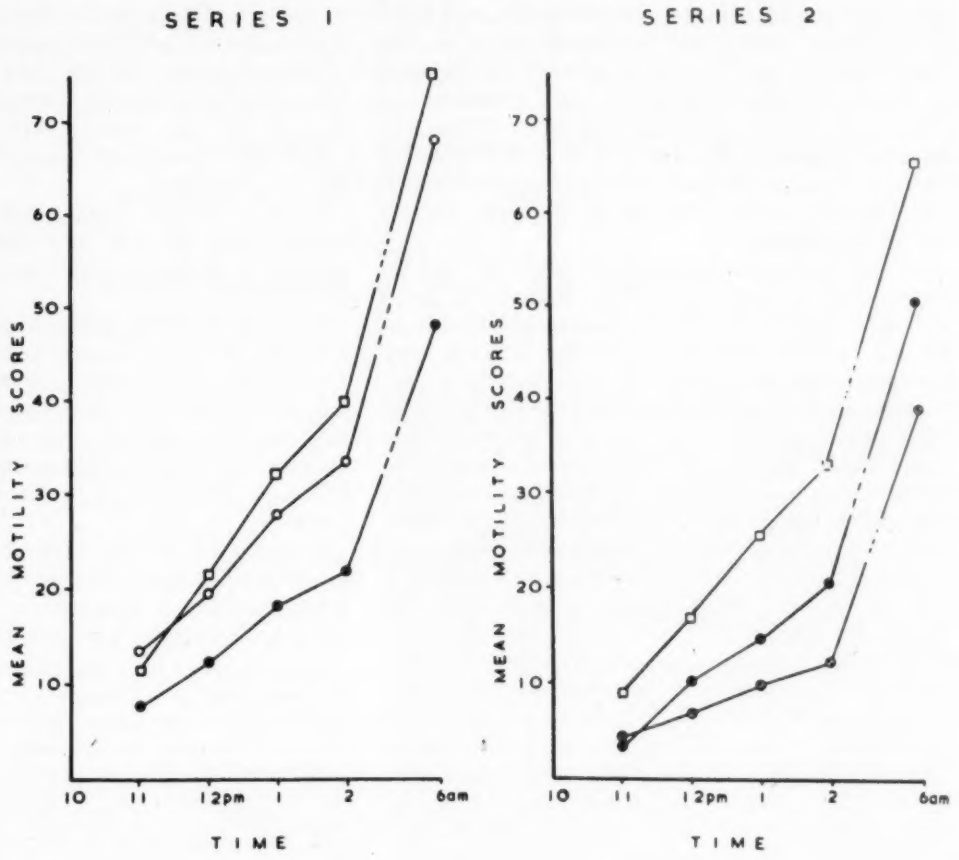

FIG. 1.—Mean motility scores at 11 and 12 p.m. and at 1, 2, and 6 a.m. for 11 patients. (Series 1: □——□ = placebo; ○——○ = 400 mg. meprobamate; ●——● = 800 mg. meprobamate. Series 2: □——□ = placebo; ●——● = 800 mg. meprobamate; ⊘——⊘ = 200 mg. pentobarbitone sodium.

(Table II). For Series 2, patients stated that they slept longer after 200 mg. pentobarbitone sodium and 800 mg. meprobamate as compared with placebo (question 2), sleep also being sounder (question 3) with these two than with placebo (Table II).

Discussion

The perfect solution to the problem of measuring depth of sleep remains elusive, and although observations by nurses of the wide-awake or snoring patient are reliable, intervening sleep levels are difficult to determine. Techniques such as shining a light on the patient (Straus, Eisenberg, and Gennis, 1955) have disadvantages, while subjective ratings by the patient may or may not agree with the nurses' evaluation of his sleep (Hare, 1955; Imboden and Lasagna, 1956). In the group of patients we studied, a subjective appraisal alone might have been misleading, for the patients with more severe mental illness were unable to complete the sleep questionnaire. Least weight should be attached to data derived from the questionnaire, as Glaser (1953 1954) and Glaser and Whittow (1953) have shown that repeated completion of questionnaires may diminish the number of responses scored on them giving a false impression in such a case of habituation to the drug. Moreover, in the previous investigation, no correlation was found between the motility scores and the patients' own estimate of sleep (Cox and Marley, 1959).

The objective findings in Series 1 of the drug trial are that 800 mg. but not 400 mg. meprobamate significantly reduces motility during sleep or recumbency. The subjective findings, on the other hand (nurses' and patients' ratings), suggest that meprobamate at both dose levels is superior to placebo in reducing restlessness and as a hypnotic. Lasagna (1956) noted that of various agents for promoting sleep in chronically ill patients, 400 mg. meprobamate was almost as effective as 800 mg. of the drug.

In Series 2, the objective findings are that both 200 mg. pentobarbitone sodium and 800 mg. meprobamate have a definite depressant action on motility, pentobarbitone being superior to meprobamate. The first part of the subjective results (nurses' ratings) are in agreement. However, from the patients' total ratings, pentobarbitone sodium but not 800 mg. meprobamate appeared to have

significant action, although paradoxically analysis of the patients' ratings for individual items on the questionnaire suggests that both drugs are superior to placebo in enhancing duration and soundness of sleep. Lasagna demonstrated that either 400 mg. or 800 mg. meprobamate was as effective as 100 mg. or 200 mg. phenobarbitone as a hypnotic, but less effective than either 100 mg. or 200 mg. quinalbarbitone sodium.

In both series, no significant effect of the drug on motility was detected until 150 minutes (12 p.m.) after administration, that for Series 1 being due to 800 mg. meprobamate and for Series 2 attributable to pentobarbitone sodium.

Inasmuch that motility during sleep and depth of sleep are at least partially correlated (and in this investigation there was a significant correlation between motility scores and the nurses' rating in both Series and between motility scores and patients' ratings of sleep in Series 2) the results are consistent with the notion that 800 mg. meprobamate possesses weak hypnotic action and reduces restlessness during sleep, although in both respects it is much less effective than 200 mg. pentobarbitone sodium. The smaller dose (400 mg.) of meprobamate seems also to possess a mild hypnotic effect but had no significant action on restlessness during sleep. Our results were obtained from patients with severe sleep disturbance, and it may be that both 400 mg. and 800 mg. meprobamate would exert a more pronounced hypnotic effect in subjects with milder insomnia.

Summary

Eleven psychiatric patients with marked insomnia were prescribed in random order 400 mg., 800 mg. meprobamate, and placebo (Series 1), and 200 mg. pentobarbitone sodium, 800 mg. meprobamate, and placebo (Series 2).

Measurements of motility during sleep were obtained from an electronic recording unit attached to the bed. The patients' sleep was rated also by the nurses and the patients themselves.

Meprobamate, 800 mg., but not 400 mg., significantly reduced motility scores in Series 1. In Series 2, both 200 mg. pentobarbitone sodium and 800 mg. meprobamate significantly diminished restlessness during sleep.

From the nurses' ratings, 200 mg. pentobarbitone sodium and 400 mg. and 800 mg. meprobamate exerted a significant hypnotic action as compared with placebo.

As judged by the patients' total ratings, 400 mg. and 800 mg. meprobamate improved sleep in Series 1 but only pentobarbitone in Series 2. Analysis of individual items from the sleep questionnaire indicated that all drugs used prolonged sleep as compared with placebo, but that sleep was only sounder after 800 mg. meprobamate or 200 mg. pentobarbitone sodium.

It is contended that both 400 mg. and 800 mg. meprobamate possess weak hypnotic activity, that 800 mg. reduces restlessness, but that in both respects 200 mg. pentobarbitone sodium is superior.

We take pleasure in thanking Dr. D. L. Davies for suggesting the investigation and for his interest and encouragement throughout. We would also like to thank Dr. A. E. Maxwell for invaluable statistical advice, the nursing staff of Ward 4, in particular Sister H. Hynes and Mr. D. Hodge, Mr. W. Brookes, the pharmacist, for his assistance, Mr. D. A. Green for photographing the stencil, and also Lederle Laboratories Division for supplying " miltown " tablets and the placebo.

References

Berger, F. M. (1954). *J. Pharmacol.*, **112** 413.
Borrus, J. C. (1955). *J. Amer. med. Ass.*, **157** 1596.
Cox, G. H., and Marley, E. (1959). *J. Neurol. Neurosurg. Psychiat.*, **22**. 57.
Glaser, E. M. (1953). *Brit. J. Pharmacol.*, **8**, 187.
—— (1954). *Clin. Sci.*, **13**, 199.
—— and Whittow, G. C. (1953). *J. Physiol (Lond).*, **122**, 43P.
Hare, E. H. (1955). *Brit. J. prev. soc. Med.*, **9**, 140.
Imboden, J., and Lasagna, L. (1956). *Bull. Johns Hopk. Hosp.*, **99**, 91.
Lasagna, L. (1956). *J. chron. Dis.*, **3**, 122.
Ludwig, B. J., and Piech, E. C. (1951). *J. Amer. chem. Soc.*, **73**, 5779.
Straus, B., Eisenberg, J., and Gennis, J. (1955). *Ann. intern. Med.*, **42**, 574.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 141.

PARAPLEGIA CAUSED BY EXTRASPINAL METASTASIS FROM A UTERINE FIBROID

BY

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Uterine fibroids are usually benign tumours, but occasionally, like some apparently benign thyroid tumours, they fail to behave as such and metastasize. "Benign metastasizing fibroid," like "benign metastasizing goitre" (Cohnheim, 1876), is a bad term, however, because it is self contradictory.

There is evidence that the thyroid tumours are carcinomas and areas may be found in them where there has been invasion of blood vessels (Bell, 1924; Graham, 1925). Similarly the apparently innocent fibroid which metastasizes may, if minutely examined, be found to have the appearance of a sarcoma. Steiner (1939) reports a case with a benign appearance in the primary tumour and in the secondary deposit, but careful examination of the former showed invasion of veins. Occasionally, however, thorough examination of these metastasizing uterine tumours fails to reveal any typically malignant structure and the same well-differentiated and benign appearance is present in the metastases as in the primary tumour in the uterus.

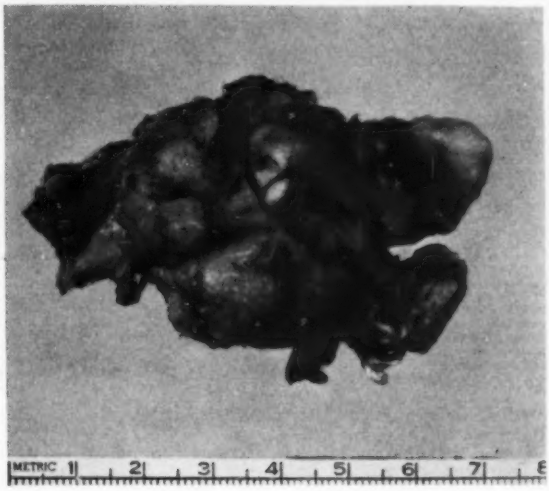

FIG. 1.—Tumour removed from sacrospinalis (weight 43 g.).

Case Report

A married woman aged 37, the mother of one child, was referred because of numbness of the right leg, unsteadiness in walking, and pain in the back radiating into the right breast. Ten years previously hysterectomy had been performed elsewhere for fibroids, and five years later leiomyomata had been removed from the abdomen and pelvis. A note at the time stated that extirpation had been incomplete and two years later a mass arising from the stump of the cervix was removed.

On examination she was found to have weakness of the legs and a diminution of all forms of sensation below the level of the nipples. The abdominal reflexes were absent, the knee and ankle jerks exaggerated, and the plantar reflexes were extensor. Several lobulated tumours could be felt in the abdomen and rectal examination showed a firm tumour involving the sacrum. Radiographs of the spine showed a bony sacral defect, but no other abnormality. Cisternal myelography showed a complete block at the level of the first thoracic vertebra.

On lumbar puncture absence of the Queckenstedt phenomenon indicated spinal block and the protein content of the fluid was 200 mg. per 100 ml. and the cell content 6 per c.mm.

At operation a lobulated tumour was exposed in the sacrospinalis (Fig. 1) and removed. Pressure from the tumour had produced smooth-edged holes in the laminae of the second and third thoracic vertebrae, through which the dura was compressed by it. The tumour was unattached to the laminae and the dura and was easily separated from its bed in the muscle mass.

The pathologist's report (Dr. W. Jones Williams, to whom we are indebted) reads:—

"Numerous blocks were examined from both lesions. The tumours of the spine and of the uterus show similar features. The appearances are those of fibroleiomyoma with no evidence of malignant change and consist of uniform whorled smooth muscle fibres admixed with fibrous tissue. No neural elements are present in either tumour, palisading is absent, and the appearances are not those of neurofibroma or neurilemmoma.

"In view of the fact that the spinal tumour may be a metastasis from the uterus both lesions were subjected to histological grading as if they were uterine sarcoma (Jones Williams and Bancroft-Livingston, 1952). On the criteria used in their article both lesions fall into the

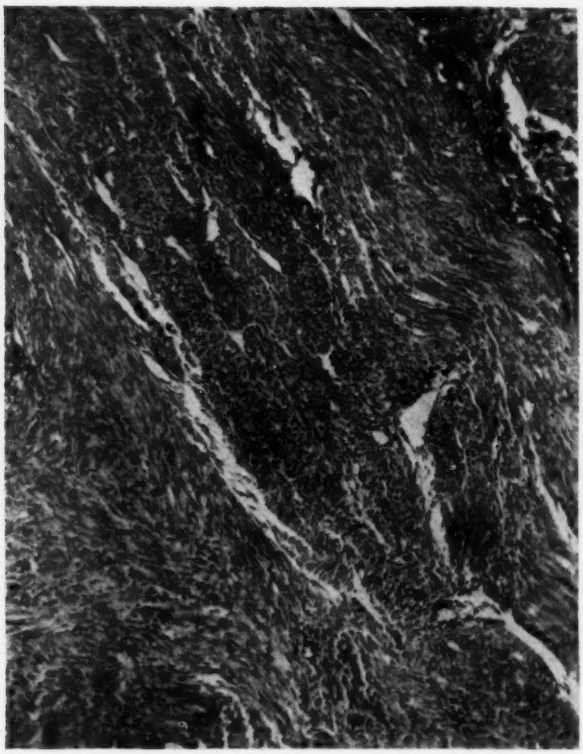

FIG. 2.—Microscopical appearance of spinal tumour ×106.

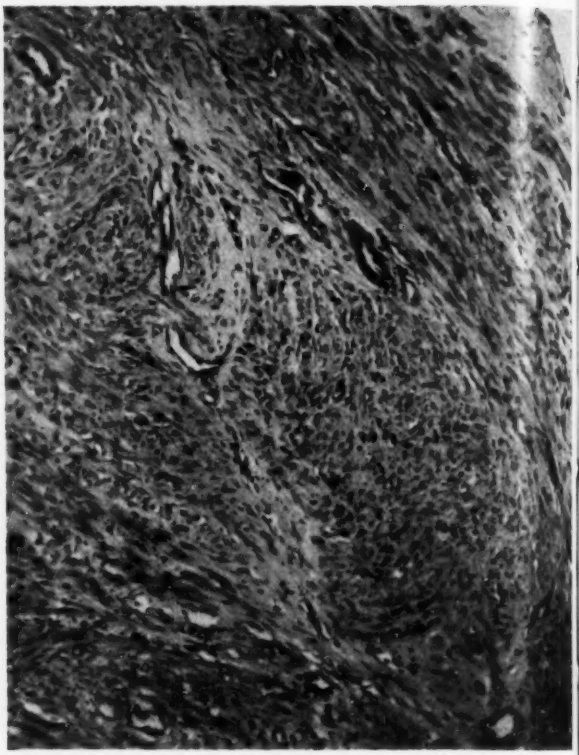

FIG. 3.—Microscopical appearance of original uterine tumour ×106.

group with the lowest grade of malignancy. In particular they show one mitosis per 25 high-power field and with no blood spaces lined by tumour cells.

"The close similarity of the uterine and spinal lesions (Figs. 2 and 3) characterized by the uniform whorled appearance with absence of the usual features of malignancy supports the view that both lesions have the appearances of benign fibroleiomyoma."

In the year which has elapsed since the laminectomy the patient has made a complete recovery from the paraplegia and has put on weight; she remains well. There are still tumours to be felt in the abdomen and at some time a further attempt may be necessary to remove them.

Comments

Leiomyosarcoma of the uterus occurs in less than 2% of leiomyomata (Wheelock and Warren, 1942) and the histology of such tumours is in most cases characteristic of malignancy. Metastasis is uncommon, the lungs being the principal site, though deposits have been found in the liver, vertebral body, and pelvis (Robbins, 1943).

The present case is unusual, inasmuch as an apparently benign uterine leiomyoma had metastasized and an extraspinal deposit of tumour in the sacrospinalis muscle mass had caused paraplegia from pressure atrophy of the subjacent laminae and compression of the cord. There was no evidence that the tumour had invaded bone. The production of round smooth defects in the vertebral laminae by the pressure of a tumour lying outside the spine must be very rare. Finally the apparently benign histological appearance of the primary tumour was also seen in the secondary deposit.

Summary

A case is recorded of metastasis from a uterine fibroid of benign appearance in a woman aged 37 in whom paraplegia was produced by pressure from a metastasis in the substance of the sacrospinalis. This tumour had produced pressure atrophy of the laminae which it overlay and had compressed the theca through the resulting laminal defects. Recovery followed removal of the tumour. Neither primary nor secondary tumours had any histological evidence of malignancy.

REFERENCES

Bell, F. G. (1924). *Brit. J. Surg.*, **12**, 331.
Cohnheim, J. (1876). *Virchows Arch. path. Anat.*, **68**, 547.
Graham, A. (1925). *Ann. Surg.*, **82**, 30.
Robbins, L. L. (1943). *Arch. Surg. (Chicago)*, **47**, 463.
Steiner, P. E. (1939). *Amer. J. Path.*, **15**, 89.
Wheelock, M. C., and Warren, S. (1942). *Ann. Surg.*, **116**, 882.
Williams, W. Jones, and Bancroft-Livingston, G. (1952). *Brit. J. Cancer*, **6**, 345.

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NEUROLOGICAL ASPECTS OF LEPTOSPIROSIS

BY

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Since leptospirosis begins with a septicaemic stage, during which leptospirae may be isolated from the cerebrospinal fluid, the occurrence of lesions in the nervous system is not unexpected. Evidence of neurological abnormality can frequently be detected in the course of a typical attack of the disease, but it is usually insignificant compared with the involvement of other organs, and has little effect on the course or outcome of the infection.

As the world-wide distribution of leptospirosis is becoming realized, however, more clinical varieties are appearing, in some of which the nervous lesions are the dominant or the only changes. These cases have not usually been jaundiced, and the infection has been caused by leptospirae other than *L. icterohaemorrhagiae*.

A summary of the previous literature is followed by a description of the neurological complications arising in 64 personally studied cases in Malaya. All cases were proved by blood culture, positive serology, or both, and were due to a variety of leptospiral types, of which the commonest were *L. pyrogenes, L. hebdomidis, L. canicola, L. grippotyphosa, and L. schüffneri.*

Observations in the Literature

The initial stages of leptospirosis are marked in over half the cases by severe headache, photophobia, and neck ridigity (Broom, 1951). Cerebrospinal pleocytosis may accompany clinical evidence of meningitis or may occur alone (Davidson and Smith, 1939; Cargill and Beeson, 1947). Rarely meningeal symptoms with optic neuritis may follow weeks or months after the initial infection (Murgatroyd, 1937).

It has been known for 40 years that leptospirosis may present as a purely meningitic illness (Costa and Troisier, 1917), and leptospiral infection accounts for a small but definite percentage of cases of benign lymphocytic meningitis (Adair, Gauld, and Smadel, 1953). Many such cases in Europe have been traced to *L. canicola*, but can also be caused by numerous other strains (van Thiel, 1948). Meningitis cases seem to be especially common after bathing, a fact which has been thought to indicate a special portal of entry via the nasopharynx (Buzzard and Wylie, 1947), but which is probably related more to the age of the patient (Broom, 1958).

The cellular reaction in the cerebrospinal fluid may be polymorphonuclear at first, but later lymphocytes predominate (Costa and Troisier, 1917). Values for protein may show a small increase, but those for chloride and glucose are normal. The urea content is commonly raised (Robertson, 1946) in proportion to the blood level. Bile-staining may occur in icteric cases, an unusual finding in jaundice from other causes.

Lesions of the peripheral nerves and plexuses, usually of the upper limb, are not uncommon. The clinical features are pain, muscle weakness, and loss of tendon reflexes. The resemblance to anterior poliomyelitis or neuralgic amyotrophy may be close (Ramsey, 1955; Middleton, 1955).

Cranial nerve involvement has been noted on a few occasions, resulting in ocular, facial, or palatal palsies of a transient nature (Scheid, 1949). Mental confusion or even psychosis may occur (Murgatroyd, 1937; Kernohan, 1956), usually at the time of the initial illness and possibly aggravated by avitaminosis. Hemiparesis (Doherty, 1956) and subarachnoid haemorrhage (Buzzard and Wylie, 1947) are rarities.

The literature contains only nine cases of spinal cord involvement (Creyx, Georget, and Bonnel, 1935; Labbé, Boulin, Uhry, and Ullman, 1935; Joosten, 1936; Hegler, 1936; Fontan, Dupin, and Verger, 1938; Mortenson, 1940). Symptoms are mainly motor, involving the legs and often accompanied by retention of urine. The outcome may be fatal (Labbé *et al.*); recovery may be uneventful (Creyz *et al.*) or slow and incomplete (Hegler). The strain of leptospira involved is variable.

Meningitis

Meningitis Complicating Leptospirosis.—Of 64 patients examined, all complained of headache

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during the initial febrile illness. In addition 19 patients (30%) complained of photophobia and 34 (54%) had some degree of nuchal rigidity. Eleven patients (18%) had nuchal rigidity of a degree sufficient to warrant a clinical diagnosis of meningitis, and in these patients lumbar puncture was carried out partly to exclude the presence of a purulent meningitis, partly to establish the nature and frequency of cerebrospinal fluid changes, and partly as a therapeutic measure to relieve the headache.

The findings in the 11 cases are summarized in Table I.

TABLE I

C.S.F. FINDINGS IN 11 CASES OF LEPTOSPIROSIS COMPLICATED BY MENINGEAL FEATURES

Case No.	Day of Disease	Fluid	Cells per c. mm.	% Polymorphs	% Lymphocytes	Protein (mg./100 ml.)
14	8	Turbid	120	80	20	35
55	7	Turbid	200	0	100	80
50	7	Turbid	60	20	80	120
51	2	Clear	4	—	—	35
48	6	Clear	1	—	—	50
42	4	Clear	1	—	—	20
40	7	Clear	2	—	—	30
39	4	Clear	1	—	—	50
29	20	Clear	2	—	—	30
	Relapse 30	Clear	4	—	—	45
	Relapse					
45	4	Clear	4	—	—	30
1	3	Clear	4	—	—	45

With one exception (Case 29) lumbar puncture was performed during the initial stage of the illness at the time when meningitic signs and symptoms were at a maximum. Cerebrospinal fluid pleocytosis was found in three out of 11 cases, and slight elevation of the protein (>40 mg. per 100 ml.) level in a further four. Chloride and glucose values (not included in Table I) were normal. Case 29 developed marked meningitic signs and symptoms during a relapse in the third and fourth weeks of illness, but no abnormality was found in the cerebrospinal fluid. Headache, anaemia, and general lassitude persisted for eight weeks.

With the exception of Case 29 meningitic symptoms were transient, lasting two to six days and going on to complete recovery.

These findings are in agreement with those of previous workers. The predominance of polymorphs in the differential cell count in Case 14 is noteworthy. The slight elevation of protein in Cases 1, 29, 39, and 48 may be within the limits of laboratory error, and so of no significance.

Meningitis as Dominant Feature (Meningitis Leptospirosa).—Three cases presented with an illness which was predominantly meningitic, the nature of which was recognized only in the light of routine serological testing.

Case 58.—This patient, a man, aged 19, was admitted on January 12, 1956, the second day of illness, complaining of severe headache, backache, and photophobia. Ten days previously he had been duck shooting in swampy ground, his legs being immersed in water for some hours at a time, but the rest of his body had remained dry. On examination his temperature was 102°F. and his pulse 110 per minute. He had marked rigidity of the neck and back, the fauces were congested, the calf and thigh muscles were tender, and the spleen tip was palpable. There was no conjunctival or ciliary injection and no abrasions or jungle sores on the legs. The knee and ankle jerks were absent and there was weakness of all muscle groups in the lower limbs, maximal in the quadriceps and plantar flexors of the foot.

A blood count showed: white blood cells 6,800 per c.mm. (polymorphonuclears 60%, lymphocytes 36%, monocytes 4%). A trace of protein was found in the urine. The serum bilirubin level was 0·6 mg. per 100 ml., blood urea 40 mg. per 100 ml. The C.S.F. (fourth day of disease) contained 110 cells per c.mm. (all lymphocytes), 90 mg. protein per 100 ml., 50 mg. glucose per 100 ml., 720 mg. chlorides per 100 ml. A blood culture was positive.

Anterior poliomyelitis was diagnosed, and treatment was on symptomatic lines only.

The patient was febrile for 48 hours after admission and had a slight secondary fever of 99·2°F. on the fourth day. Weakness and tenderness of all muscle groups in both lower limbs was present for one week. The knee and ankle jerks returned after five days, but remained sluggish for two weeks, by which time symptomatic recovery was complete. There were no sequelae.

Case 56.—This Gurkha soldier, aged 26, was seen on September 28, 1955, the sixth day of illness, complaining of headache, severe pain in the legs, neck stiffness, vomiting, and slight abdominal pain. For the previous three weeks he had been engaged in jungle ambush work in the Ipoh area under damp conditions. His temperature was 104°F. and pulse 110 per minute. There were no abnormal physical signs apart from nuchal rigidity and muscular tenderness. Small jungle sores were noted on the shins.

A blood count showed: white blood cells, 11,200 per c.mm. (polymorphonuclears 92%, lymphocytes 8%). The urine contained protein +, occasional white cells, and casts. The C.S.F. (eighth day of disease) showed 8 cells per c.mm., all lymphocytes, and 60 mg. protein per 100 ml.

Complement fixation and agglutination reactions were positive.

The clinical diagnosis on admission was anterior poliomyelitis, and treatment was on symptomatic lines only.

Fever subsided after 10 days of illness and the patient was asymptomatic after two weeks. There were no sequelae.

Case 57.—This Gurkha rifleman, aged 23, in the same company as Case 56, was referred to hospital on October 3, 1955, with the complaint of headache, vomiting, and

TABLE II

SUMMARY OF C.S.F. FINDINGS IN THREE CASES OF MENINGITIS LEPTOSPIROSA

Case No.	Day of Disease	Fluid	Cells	% Polymorphs	% Lymphocytes	Protein (mg. per 100 ml.)	Chloride (mg. per 100 ml.)	Glucose (mg. per 100 ml.)
58	4	Turbid	110	—	100	90	720	50
56	8	Clear	8	—	100	60	—	—
57	7	Turbid	280	80	20	85	720	45
	14	Clear	1	—	—	30	—	—

cough for six days. On examination his temperature was 101°F. and pulse 70 per minute. He appeared drowsy and confused with marked nuchal rigidity and muscular tenderness in the legs. The knee and ankle jerks were sluggish.

A blood count showed: white blood cells 10,300 per c.mm. (polymorphonuclears 84%, lymphocytes 10%, monocytes 6%). The urine appeared normal. The C.S.F. (seventh day of disease) contained 280 cells per c.mm. (polymorphonuclears 80%, lymphocytes 20%), 85 mg. protein per 100 ml., 45 mg. glucose per 100 ml., and 720 mg. chlorides per 100 ml. On the fourteenth day of disease cells had fallen to 1 per c.mm., and protein to 30 mg. per 100 ml. Complement fixation and agglutination reactions were positive.

The clinical diagnosis on admission was anterior poliomyelitis, and treatment was on symptomatic lines only.

The fever continued for 36 hours after admission, and there were no symptoms or signs after three days. Tendon reflexes returned to normal and there were no sequelae.

These cases illustrate the value of routine serological testing in patients with lymphocytic meningitis. There was little to suggest a diagnosis of leptospirosis on admission, although it is significant that two of the three cases had proteinuria.

Peripheral Nerve Lesions

Two patients presented unequivocal evidence of peripheral neuritis during the course of leptospirosis.

Case 48.—This man, aged 24, suffered a mild attack of leptospirosis, being febrile for nine days. He was admitted on the fourth day of illness, at which time neck stiffness was a prominent sign and lumbar puncture was performed, the fluid being normal. During the acute phase of the illness and for five days after the fever had subsided he complained of severe neuralgic pain in the distribution of the fifth and sixth cervical nerves on the right side. He also complained of pain and numbness in both lower limbs for the first three days. Tendon reflexes were diminished in the right arm and there was some weakness of the triceps muscle on that side, but no sensory loss and no objective findings in the legs. Complement fixation and agglutination reactions were positive.

Treatment was symptomatic and recovery was complete in two weeks.

Case 29.—This patient, aged 28, was admitted on May 10, 1955, with a moderately severe attack of leptospirosis, being febrile for 14 days and having a relapse with meningism during the fourth week. On the fifteenth day of illness he developed paraesthesiae in both feet which lasted for five days. This was succeeded by a severe aching pain over the distribution of the fourth and fifth cervical nerves on the left side. There was weakness of the deltoid and biceps muscles on that side and the biceps and supinator reflexes were diminished. No sensory loss was demonstrable.

Complement fixation and agglutination reactions were positive.

Treatment was symptomatic and recovery was complete in six weeks.

The clinical syndrome in the above cases is similar to neuralgic amyotrophy which may follow serum injections. The lesion may be in the brachial plexus.

A Case of Spinal Involvement

One case was complicated by an ascending myelitis of an extent not previously reported. Full details are therefore given.

Case 64.—The patient, aged 19, was in good health until May 11, 1956, when during a jungle patrol he developed a severe frontal headache, diarrhoea, and fever. After three days he came out of the jungle and was seen by the regimental medical officer, who immediately arranged his admission to hospital. On arrival his general condition was poor. He was unable to sit up and complained of headache and abdominal pain. His temperature was 101°F. and his pulse 90 per minute. There was marked conjunctival and scleral injection, acutely tender calf muscles, scattered rhonchi over both lung fields, and ill-defined tenderness in the right upper quadrant of the abdomen. Slightly enlarged, painless lymph nodes were palpable in all areas. The provisional diagnosis was leptospirosis. The haemoglobin was 11·9 g.%, white blood cells 15,200 per c.mm. (polymorphs 80%, lymphocytes 20%). Blood urea was 75 mg. per 100 ml. On the evening of the day of admission he was noticed to have a mild degree of neck stiffness and slight weakness of the legs, affecting all the muscle groups. The tendon reflexes were present and equal. He had some difficulty with micturition and the bladder was palpably enlarged.

On the following day the neck stiffness was more pronounced and the muscular weakness had spread to involve the trunk and arms, the legs still being more severely affected. Reflexes were just obtainable and there was no sensory loss. Coordination in the arms was normal but could not be tested in the legs owing to the weakness. He was mentally clear but extremely anxious. Coarse nystagmus was present on lateral gaze, but apart

from this the cranial nerves appeared normal. Respirations were rapid and shallow and towards evening were clearly becoming inadequate; no movement was appreciable in the lower part of the chest and the accessory muscles of respiration were active. There was slight central cyanosis. Swallowing and speaking were unaffected at this stage, and blood pressure was well maintained. He had by this time developed acute retention of urine and required intermittent catheterization. Twenty-four hours after admission he was placed in a Drinker respirator, and after a short period of alarm he was able to adapt himself to its movements.

At this time he was thought to have anterior poliomyelitis or acute infective polyneuritis, and after 36 hours it was clear that the upward spread of paralysis was still progressing. For a period of six hours his speech was affected, becoming weak and nasal in quality, and swallowing was achieved only with slight choking and spluttering. There was almost complete paralysis of respiration, which unaided took the form of irregular diaphragmatic gasping contractions every five to 10 seconds. There was no intercostal element, and the respirations were accompanied by a marked tracheal tug.

The respirator was tilted head-down at an angle of 15° and the posterior pharynx aspirated at intervals, but paralysis of swallowing was never complete enough to make pooling of secretions a major problem.

Apart from this evidence of bulbar damage he developed a defect of conjugate lateral movement of the eyes. Although he appeared confused and slightly euphoric there was no marked disturbance of consciousness, and he complained of cramps in the limbs and abdominal pains, which were ascribed to spasm of the abdominal muscles. He lay with legs extended and feet plantarflexed, arms flexed at elbow and wrist, and with adduction and internal rotation at the shoulder. A constant coarse fasciculation was present in the muscles of the shoulder girdle, and there was sometimes a coarse clonic twitching in the pectoralis major on both sides, violent enough to move the whole upper limb. Muscle tone was diminished in all but the pectoral group, power was grossly reduced, tendon reflexes in all limbs were lost, and plantar responses were extensor. Bladder control was still defective, and an indwelling catheter was introduced, urine being released every four hours. All modalities of sensation were diminished over the lower part of the body, an ill-defined sensory level being present at the costal margin.

In summary, there was evidence of an acute infection of the spinal cord spreading in the course of 48 hours to involve the medulla and mid-brain, and affecting the motor neurones, long sensory tracts, and pyramidal fibres.

Treatment at this stage was supportive, and aimed at the prevention of skin, pulmonary, and urinary complications, but in spite of prophylactive sulphonamides and a large fluid intake he developed a *Bact. coli* infection of the urinary tract which was difficult to eradicate. A careful watch was kept on the cardiovascular system, but apart from a constant tachycardia of 100 to 110 there were no other signs and the blood pressure remained steady at a normal figure.

After progressing rapidly for 48 hours the paralysis began to recede slowly. The patient was taken out of the respirator for increasing periods each hour, and by the fourth day was fit enough to breath without it. Power slowly returned to his limbs and the tendon reflexes reappeared. The trunk muscles regained their tone, and by the tenth day he was able to sit up. Perception to pin-prick remained diminished in the legs for 10 days.

At the end of a month there was only a slight generalized diminution of muscle power, but the urinary infection persisted and resulted in the formation of a urethral stricture which eventually required surgical treatment. He also had a mild residual normochromic anaemia (haemoglobin 10·1 g.%). Examination of the cerebrospinal fluid after six weeks showed no abnormality apart from a raised protein level (90 mg. per 100 ml.).

Fletcher's culture for leptospirosis was performed on the blood at the time of admission and was read at 15 and 25 days, leptospirae being seen on both occasions. Unfortunately the culture became secondarily infected, and further identification of the serological type of the organism was not then possible.

TABLE III

C.S.F. FINDINGS IN CASE 64

Day of Disease	4	16	42
Appearance	clear	clear	clear
Cells (per c.mm.)	25	1	1
Polymorphs (%)	60	—	—
Lymphocytes (%)	40	—	—
Protein (mg. per 100 ml.)	110	124	90
Chlorides (mg. per 100 ml.)	720	740	740
Glucose (mg. per 100 ml.)	43	46	70

Culture of the cerebrospinal fluid on blood-agar was sterile on all occasions.

Serological specimens were taken on the ninth, 16th, and 25th days, and were tested at the Wellcome Laboratories, using the agglutination technique. The ninth and sixteenth day specimens were positive to 1 in 100 with the following strains: *L. autumnalis*, *L. bangkinang*, *L. javanica*, *L. hebdomidis*, *L. pomona*. The 25th day specimen reacted with the same strains to 1 in 1,000 but were not tested to higher dilutions.

A similar rapid upward spread of the paralysis with transient brain-stem involvement sometimes occurs in acute infective polyradiculitis. Muscle fasciculation is sometimes observed in this condition, and in paralytic poliomyelitis at the time of destruction of the anterior horn cells, but seldom to such a degree as in this patient.

Had the nasopharyngeal paralysis lasted for more than a few hours secretions would probably have been inhaled. Probably better treatment would have been an elective tracheotomy at an earlier stage and insertion of a cuffed endotracheal tube.

Discussion

One of the striking features in the literature and the cases reported here is the extent of neurological damage which is compatible with complete recovery.

Even the most complete and extensive paralysis, as in Case 64, appears to carry a good prognosis if the patient can be kept alive during the initial stages.

The nature of the neurological lesions must remain in doubt. In a disease characterized by a haemorrhagic tendency it might be expected that complications of a vascular nature would occur. With the possible exception of peripheral neuritis, which has been ascribed to haemorrhage into the nerve sheaths (Kramer, 1926), none of the cases described in the present series has any features to suggest single haemorrhage from a large vessel or multiple haemorrhage from small vessels, and apart from the case with subarachnoid haemorrhage described by Buzzard and Wylie (1947) and the hemiplegic patient mentioned by Doherty (1956), vascular lesions are conspicuously lacking in the literature.

Clinical and pathological evidence of acute meningitis in the initial stages is a common finding and is attributable to the presence of leptospirae in the cerebrospinal fluid. However, in the few cases of leptospirosis with neurological involvement which have come to necropsy, there has been no suggestion of a progressive exudate or fibrotic process such as occurs in pyogenic or tuberculous meningitis. van Thiel (1948) has suggested that leptospirae are unable to proliferate in the meninges.

Changes in the parenchyma of brain, brain-stem, and spinal cord are equally inconspicuous. Leptospirae have been demonstrated in the cerebral cortex (Bingel, 1936), and occasionally microscopic evidence of inflammation with nerve cell degeneration similar to that seen in encephalitis lethargica (Koppisch and Bond, 1952), but the usual finding is minimal perivascular infiltration with lymphocytes in the hippocampus, medulla, cerebellum, and basal ganglia. Neither anterior horn cell damage nor demyelination is evident.

There is, however, some clinical resemblance between certain of the neurological sequelae of leptospirosis, notably myelitis, and the nervous complications of smallpox, measles, varicella, vaccination, or other prophylactic inoculations, all of which have been ascribed to a non-specific allergic reaction of the nervous system to various antigens, chiefly bacterial or viral (Miller and Evans, 1953), and have been reproduced experimentally (Lumsden, 1949).

Points of similarity between these post-infective encephalo-myelitides and the sequelae of leptospirosis are the latent interval after infection, the rapid onset of widespread spinal damage, the relatively small meningeal reaction, and the possibility of complete recovery. However, the absence of drowsiness, convulsions, other signs of encephalitis, and the lack of histological evidence of demyelination in fatal cases does not support such a theory (Koppisch and Bond, 1952).

The case of ascending mesencephalomyelitis described in the present series is of a type not previously reported. The paralysis spread rapidly to involve the respiratory muscles and motor cranial nerves in medulla and brain-stem as high as the mid-brain. The disease bore some resemblance to acute infective polyradiculitis in its rapid symmetrical onset and upward spread, its predominance of motor over sensory involvement, and the high protein levels in the cerebrospinal fluid. Against this were the absence of facial involvement, the occurrence of external ophthalmoplegia, the marked sphincter disturbance, the presence of extensor plantar responses, and the relatively rapid recovery, all unusual features of polyradiculitis.

The fact that full recovery can occur in this condition makes management of the paralysed patient all the more important, since faulty treatment may be worse than no treatment at all. This is particularly the case if bulbar weakness supervenes on diaphragmatic and intercostal paralysis, when assisted respiration of the type provided by the standard tank respirator may aspirate pharyngeal secretions into the lungs. In the present case, although a slight degree of palatal weakness developed, there was no serious interference with the swallowing mechanism. Tipping the patient with frequent aspiration of the pharynx were sufficient to prevent accumulation of secretions during the short period of bulbar paralysis.

Should the paralysis persist, however, experience with poliomyelitis in Denmark and elsewhere has shown that the ideal treatment for the combined respiratory and pharyngeal form is early tracheotomy with intermittent positive pressure respiration (Smith, Spalding, and Russell, 1954). There is no danger of inhalation and the arrangement permits of easy aspiration of the trachea and bronchi. Such treatment could be life-saving on the rare occasions when leptospirosis is complicated by spinal cord and brain-stem involvement.

Summary

The various types of neurological disorders occurring in leptospirosis are reviewed from previous reports. There are four main groups in order of frequency:

(*a*) Meningitis which may be early or late and may occur either as a secondary complication of an attack of leptospirosis or as the primary feature of the illness.

(*b*) Peripheral nerve lesions, usually a late complication, affecting the proximal muscles of the upper limbs.

(*c*) Cortical and cranial lesions, rare and unimportant features usually occurring in severe infections.

(*d*) Spinal cord lesions, which are also rare and consist of transverse or ascending forms of myelitis.

The neurological lesions in the present series are described. There were 11 cases with symptoms and signs suggestive of meningitis, which occurred during a typical attack of leptospirosis. Three had cerebrospinal pleocytosis and in a further four the cerebrospinal fluid protein level was raised.

Three cases of meningitis leptospirosa are described in which the illness was predominantly meningitic throughout.

Two cases of peripheral neuritis are described, both affecting the upper limbs.

One case of rapidly ascending mesencephalomyelitis affecting the motor and sensory functions of the spinal cord and brain-stem as high as the mid-brain is described.

All patients recovered completely from the neurological sequelae.

The manner in which leptospirosis damages the nervous system is discussed.

The acute inflammatory reaction is a result of the invasion of the meninges by leptospirae. The inflammation is lymphocytic and is not followed by fibrosis.

There is little to favour a vascular aetiology in the later neurological complications. However, there are some features of myelitis which suggest that it may be an allergic response on the part of the nervous system.

The management of patients with bulbar lesions is briefly discussed, and early treatment with a mechanized positive pressure respirator combined with tracheotomy is recommended.

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References

Adair, C. V., Gauld, R. L., and Smadel, J. E. (1953). *Ann. intern. Med.*, **39**, 675.

Bingel, A. (1936). *Dtsch. Z. Nervenheilk.*, **141**, 133 (quoted by Mortenson, 1940).

Broom, J. C. (1951). *Brit. med. J.*, **2**, 689.

—— (1958). Personal communication.

Buzzard, E. M., and Wylie, J. A. H. (1947). *Lancet*, **2**, 417.

Cargill, W. H., and Beeson, P. B. (1947). *Ann. intern. Med.*, 27, 396.

Costa, S., and Troisier, J. (1917). *Presse méd.*, **25**, 189.

Creyx, A., Georget, P., and Bonnel, H. (1935). *J. Méd. Bordeaux*, **112**, 527.

Davidson, L. S. P., and Smith, J. (1939). *Brit. med. J.*, **2**, 414.

Doherty, R. L. (1956). *Aust. Ann. Med.*, **5**, 23.

Fontan, A., Dupin, J., and Verger, P. (1938). *J. Méd. Bordeaux*, **115**(1), 497.

Hegler, C. (1936). *Dtsch. Z. Chir.*, **248**, 190.

Joosten, A. J. (1936). *Ned. T. Geneesk.*, **80**, 1821.

Kernohan, R. J. (1956). *Brit. med. J.*, **1**, 1342.

Koppisch, E., and Bond, W. M. (1952). Section of Pathology, Symposium on the Leptospiroses. Army Med. Service Graduate School. Walter Reed A. M. C., Wash., D.C.

Kramer, P. H. (1926). *Ned. T. Geneesk.*, **70**(2), 1942 (quoted by Walch-Sordrager, 1939).

Labbé, M., Boulin, R., Uhry, P., and Ullman, B. (1935). *Bull. Soc. méd. Hôp., Paris*, **59**, 1504.

Lumsden, C. E. (1949). *Brain*, **72**, 198.

Middleton, J. E. (1955). *Brit. med. J.*, **2**, 25.

Miller, H. G., and Evans, M. J. (1953). *Quart. J. Med.*, **22**, 347.

Mortenson, V. (1940). *Lancet*, **1**, 117.

Murgatroyd, F. (1937). *Brit. med. J.*, **1**, 7.

Ramsey, A. M. (1955). *Ibid*, **2**, 24.

Robertson, K. (1946). *Ibid*, **2**, 810.

Scheid, W. (1949). *Fortschr. Neurol. Psychiat.*, **17**, 295.

Smith, A. C., Spalding, J. M. K., and Russell, W. R. (1954). *Lancet*, **1**, 939.

Thiel, P. H., van (1948). *The Leptospiroses*. Universitaire Pers, Leiden.

BOOK REVIEWS

Brain—Memory—Learning: A Neurologist's View. By W. Ritchie Russell. (Pp. xii + 140; illustrated. 18*s*.) Oxford: The Clarendon Press. 1959.

In this admirable little book, Dr. Ritchie Russell aligns himself firmly with those who regard psychological issues as inseparable from the problems of neurology. "The developmental of the human mind," he points out in his Preface, " . . . probably provides the most important evidence of all about cerebral mechanisms"—and it is just this evidence which the author seeks to embody in his general conception of brain function. In particular, he has been much impressed by the evidence relating to learning in early life and its importance for later development—evidence which has been culled from sources as diverse as comparative zoology, experimental psychology, and psycho-analysis. This leads him to consider with particular care the whole problem of memory, which he traces from its comparatively simple origins in synaptic plasticity to the complex systems derived from past experience which must be assumed to operate in recognition and recall. Although the gaps in our knowledge are enormous, Dr. Ritchie Russell makes a most praiseworthy attempt to bridge them. In particular, his excellent account of the traumatic amnesias leaves no doubt as to the contribution which clinical study can make to our understanding of memory. Of great interest, too, is his attempt to link the problem of early learning with the functions of the frontal lobes. Although admittedly speculative, this suggestion would seem well worthy of more detailed inquiry.

Not unnaturally, Dr. Ritchie Russell devotes a good deal of space to aspects of neurology in which his own special research interests have lain. Thus he presents an admirably lucid account of concussion in which emphasis is placed upon the widespread distortion of hemisphere tracts rather than upon localized damage to the brain-stem. This account should do much to restore a more balanced perspective with regard to the problem of consciousness. Other chapters are devoted to the sensori-motor cortex, traumatic epilepsy, and the problem of pain. Although much of the material cited in these chapters will be already familiar to those who have followed the work of the author and his colleagues, the present account has particular value in bringing together a number of scattered contributions and in relating them to more general issues in neurology. Dr. Ritchie Russell also devotes some interesting pages to the problem of frontal lobe function and the rationale of leucotomy.

It is evident that a book which attempts to cover so much in so brief a scope cannot satisfy everybody. The present reviewer must confess to slight disappointment that the author has seen fit to devote only three and a half pages to aphasia and that apraxia and kindred disorders receive no more than passing mention. He has also the impression that the author's treatment of theoretical issues leaves something to be desired. For example, there seems to be some real confusion regarding the Jacksonian concept of "levels of function" and its relation to the anatomy and physiology of cerebral systems. So far as the present reviewer has been able to follow Jackson, there is no suggestion in his writings that "levels of function" are to be regarded as governed in any precise way by considerations of structure. If this is correct, the fact that important aspects of behaviour may depend upon subcortical no less than upon cortical structures in no way invalidates Jackson's position. Whatever the precise cerebral systems involved, say, in the activity of swearing, the latter remains less complex and more automatic than propositional speech, and to this extent demands treatment as a "lower level" function. Had Dr. Ritchie Russell given more attention to levels of psychological function, and to the correlated distinction between "negative" and "positive" sequelae of brain injury, it is possible that he would have provided an even more satisfactory neurological framework for the analysis of behaviour.

It is noteworthy that Dr. Ritchie Russell lays particular stress on the work of Freud and his disciples in providing some account of the general development of human behaviour, if from a standpoint very different from his own. One might wish that this parallel had been developed somewhat more fully. Even within neurology itself, the role of psychopathological mechanisms of the type conceived by Freud is being increasingly acknowledged, as, for example, in recent studies of anosognosia and the mechanisms of denial. A more adequate appraisal of these mechanisms from the more cautious standpoint of neurology might appear both rewarding and timely. All the same, it may be hoped that psycho-analysts and others, whose attitude to neurology has not hitherto been marked by conspicuous tolerance, will take due note of Dr. Ritchie Russell's broad-minded and generous tribute to the work of their master.

This little book will have permanent value as recording the work and views of a physician whose vision extends far beyond the day-to-day preoccupations of clinical neurology. Its author combines the broad humanity of the good physician with the almost boyish curiosity of the born investigator. If he is at times simple-minded, it is a simplicity which surprisingly often proves nearer the mark than the sophistication of the professional scientist, at all events in the somewhat arid field of modern psychology. Anyone who cares about the mind and its physical basis will read this book with enjoyment and profit.

O. L. ZANGWILL.

The Waking Brain. By H. W. Magoun. (Pp. viii + 138; 55 figures. 36*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

Every now and then some new cerebral or spinal mechanism is discovered which shows that current ideas of how things work are much too simple. The work of Dr. Magoun and his associates has been specially concerned with a study of brain-stem mechanisms which appear to facilitate or inhibit the general level of activity in the central nervous system. In this small book the author provides us with a welcome account of his reflections on these and other recently described mechanisms. It seems clear that the presence of some very remarkable mechanisns for changing thresholds have been demonstrated, and can be thrown into action by artificially stimulating certain areas in the brain-stem. These areas are now referred to as the reticular formation, but the anatomical details of the mechanism are still obscure, as also is the means whereby these threshold-changing activities are normally activated.

The History and Philosophy of Knowledge of the Brain and its Functions. Edited by F. N. L. Poynter. (Pp. x + 272; illustrated. 22*s*. 6*d*.) Oxford: Blackwell Scientific Publications. 1958.

This volume contains the papers delivered at an Anglo-American symposium held in London in July, 1957, under the auspices of the Wellcome Historical Medical Library. The 16 papers deal with various aspects of the history of thought on the function of the brain and its relationship to consciousness and mental activity, and in addition there is an address by Sir Henry Dale on Anglo-American cooperation in science and medicine.

These papers are of great interest and some of them deal with aspects of the subject on which comparatively little has been written previously, outstanding amongst these being Dr. Veith's contribution on non-western concepts of psychic function with illustrations of Tibetan medical scrolls and Professor Lewis's account of Reil's concepts of brain function.

The Brain and Human Behaviour. Proceedings of the Association for Research in Nervous and Mental Disease, Vol. xxxvi., New York, December, 1956. Edited by Harry C. Solomon, Stanley Cobb, and Wilder Penfield. (Pp. xi + 564; 200 figures, 53 tables. 120*s*) London: Baillière, Tindall & Cox. 1958.

This is volume XXXVI of an already well known and valuable series. The presentation comes well up to previous standards, and the subject matter covers a wide field of neurology and the border country of psychology. The title of the book is slightly misleading in that several papers confine their attention to animal experimentation rather than human problems, but the very fact that psychologists and neurologists have got together to discuss their experiments, whether human or otherwise, is an advance indeed. Particularly outstanding are the papers of Lashley and Denny-Brown and Chambers which may well become classics as they open a new era of neurology and psychology, binding the two together as has never previously been possible. This is a fascinating volume with a wealth of important contributions, but one would wish that the editor had insisted on more conciseness and clarity.

A Ciba Foundation Symposium on the Neurological Basis of Behaviour. Edited by Dr. G. E. W. Wolstenholme and Cecilia M. O'Connor. (Pp. xii + 400; 109 illustrations. 52*s*. 6*d*.) London: J. & A. Churchill. 1958.

In commemoration of the birth in 1857 of Sir Charles Sherrington a small international group of eminent scientists met in London in July, 1957, to discuss the accumulated neurophysiological data on behaviour disorders. Beginning with the historical development of ideas relating the mind to the brain, the ground covered includes researches into the effects on, and associations with, various forms of behaviour as a result of electrical or chemical stimulation of the brain.

This is an excellent collection of authoritative essays, and will be a valuable source of information to many.

The Sherrington Lectures V. **The Excitable Cortex in Conscious Man.** By Wilder Penfield. Liverpool. (Pp. ix + 43; 15 figures. 10*s*. 6*d*.) Liverpool University Press. 1958.

In this lecture Dr. Penfield describes many of the more dramatic of his experiences while stimulating the cerebral cortex in conscious man. The so-called "psychical" responses receive special attention and are of very wide interest.

The reader will turn with interest to the recent views of what Dr. Penfield has called the "centrencephalic" system, and the "highest level in the brain". It still, however, seems difficult to appreciate Dr. Penfield's idea. The electrical stimulus to the temporal lobe which causes a complicated sensation of illusion or hallucination, or of memory, is thought to do so by activating a contrencephalic organization. The subjective visual sensations produced by stimulating the calcarine cortex are due to transmission to this central mechanism. This conception does not seem to get us very far. One might almost imagine that this central system does far more than the cortex itself, and yet surely there is here a confusion between the fact that centrencephalic structures must be normal for all brain activity, and the fact that we are dements without the cortex. It seems to be artificial to promote the brain-stem mechanisms to such lofty heights. Nothing works without them, but by themselves they are ineffective. Phylogenetically the cerebral cortex seems to have developed as an elaboration of the brain-stem and basal ganglia, and it would seem to be fruitless to try and and separate, and to place in order of importance, structures which are so intimately a part of each other.

Autonomic Imbalance and the Hypothalamus. By Ernest Gellhorn. (Pp. xiv + 300; 101 figures, 12 tables. 68*s*.) Published for the Minnesota University Press by the Oxford University Press, London. 1958.

The hypothalamus is important as a major cerebral centre for visceral function. Recently growing physiological evidence suggests it also plays an important part

in the alerting mechanism of the cortex. As such its interest to clinical medicine and to the student of human behaviour is increased. In this book Dr. Gellhorn reviews the part played by the hypothalamus and the autonomic system in the function of the central nervous system. It is a subject he has worked on for over 20 years. In early chapters he discusses the basic neurophysiology of the autonomic system both sympathetic and parasympathetic, and the inter-relation between neuronal and hormonal control of autonomic change. He also discusses analysis of autonomic function by the action of drugs of known physiological effect. He then applies these findings to the physiology of emotional change in man, and mentions their possible applications to psychiatry. The book is stimulating and contains much useful and established facts on autonomic physiology. At times, however, the evidence is not very critically assessed and speculation is not very clearly separated from fact.

Reticular Formation of the Brain. Henry Ford International Symposium. (Pp. xiv + 766; 361 figures. 115*s*.) London: J. & A. Churchill. 1957.

This publication is a report of a symposium held in Detroit, Michigan, in March, 1957.

The discovery of pathways in the brain-stem, which are concerned with mechanisms that alert the cerebral cortex, has led to a great deal of research in recent years. It has become apparent that alerting systems are "built in" to all parts of the central nervous system, and this volume illustrates some of the many approaches that can be made to this difficult problem.

The Neurologic Examination. Incorporating the Fundamentals of Neuroanatomy and Neurophysiology, 2nd ed. By Russell N. DeJong. (Pp. 1,078; 368 figures. 140*s*.) London: Pitman Medical Publishing Co. 1958.

Since the first edition of this book (1950) neurophysiology and neuroanatomy have made very significant advances so that a revised edition was desirable. The presentation of this large volume is extremely good with its clarity of arrangement and illustration. In the preface the author states his "intent to make this work a practical guide to students and practitioners of medicine in the study of the essentials of the neurologic examination and the fundamentals of clinical neurology". Most medical students, however, would develop an acute anxiety state if confronted with this large volume, and many medical practitioners would certainly believe that neurological diagnosis is even more time consuming than it is in reality. In spite of this book being a mine of information, the experienced neurologist, using it as a book of reference, may not find an answer to his question. The neuroanatomy is dealt with clearly and simply, the neurophysiology as such is scant and is seldom more than popularized functional neuroanatomy. The references at the end of each chapter are a useful selection as an introduction to the literature.

Diseases of the Nervous System. By Sir Francis Walshe. (Pp. xvi + 373; 58 figures. 30*s*.) Edinburgh: E & S Livingstone. 1958.

This book first appeared 18 years ago and has been through nine editions since then. This certainly bespeaks a continuing popularity. Although it is directed primarily to the student and practitioner, it is of value to the neurologist for it gives the opinion of one with long clinical experience and a background of neurophysiological thinking. Its bulk has not increased greatly but it remains an up-to-date presentation of neurology. At a time when the biochemical approach to certain neurological problems is proving its value both in clinical practice and clinical investigation it is appropriate that two new chapters by Dr. John Walshe on biochemical aspects of neurology should be added. The book will continue to earn and deserve a widespread audience.

Head Injuries. Compiled by E. S. Gurdjian and J. E. Webster. (Pp. 482. $14.00.) Boston: Little, Brown and Company. 1958.

This volume reflects the experience of two neurosurgeons in the field of head injuries, and provides a practical account of many of the problems of management. As a work of reference for the unusual, however, this book is disappointing. Thus the consideration of the physical forces concerned with head injury, the traumatic amnesias, the traumatic dementias and lesions of the cranial nerves, are both superficial and inadequate.

The Relation of Psychiatry to Pharmacology. By Abraham Wikler. (Pp. viii + 322. 32*s*.) London: Baillière, Tindall & Cox. 1957.

This book is a survey of the literature of the period 1930-1955 dealing with the effects of drugs used in psychiatry in the treatment or investigation of mental illness. The second section of the book deals with theories of the mechanisms of these drugs, under three headings, biochemical, neurophysiological, and psychological.

The author has set himself a mammoth task and has had to set a limit to the number of drugs discussed. When one sees, however, that he has restricted himself to the discussion of "insulin, carbon dioxide, barbiturates and other anaesthetics, amphetamine and metamphetamine, pipradol, chlorpromazine, reserpine, meprobramate, azacyclonal, d-lysergic acid diethylamide and mescaline", other drugs being discussed only incidentally, it will be obvious that very little of importance has been omitted.

This review is intended primarily for pharmacologists but is of immense value to psychiatrists, confronted as they are with a vast and often contradictory literature regarding the efficacy of the various drugs. The sceptical approach of the author is most salutary and clinicians come in for some sharp criticisms because of their penchant for formulating theories which are logically untestable and therefore irrefutable. A review of the literature in this field was needed and when the review is as good as this it can be strongly recommended.

The material in this book was originally intended to be published in pharmacological reviews but the size of the manuscript did not allow publication in that form. The publication was subsidized by the American Society

for Pharmacology and Experimental Therapeutics so that it could be made available without delay and at as low cost as possible. It is in a paper cover but is exceedingly good value.

Psychopharmacology. Edited by Harry H. Pennes. (Pp. xiv + 362; 35 figures. 60*s*.) London: Cassell. 1958.

This symposium reviews the problems encountered in the study of the effects of drugs on the brain. There were 41 participants and every contribution reveals major difficulties in work in this special branch of pharmacology. For instance, the first chapter by Linden, Quastel, and Sved on the effects of chlorpromazine on brain metabolism *in vitro* illustrates the contrast between accurate biochemical techniques and the problem of extrapolation of the results. Dr. Asenath Petrie makes an interesting contribution on the comparison of the effects of chlorpromazine and surgical cerebral lesions. The problems of devising adequate tests are stressed by her. "We are at the stone age of personality testing." Nevertheless the comparison between the effects of chlorpromazine and frontal lobotomy is a striking one and illustrates a method of study which may be profitable in the future.

J. A. Schneider and E. B. Sigg, in a summary of the pharmacology of chlorpromazine, reserpine, and meprobamate, show the complexity of the comparative analysis of these drugs.

Throughout the symposium there is a great awareness of species differences, a hesitation to extrapolate, and a readiness to adopt new techniques for assessment of drug action in the central nervous system. These are commendable attributes. It is also clear that the subject is in a state of detailed complexity. Lack of knowledge about chemical transmission in the central nervous system and the perpetual difficulty of relating chemical structure to pharmacological action combine to bring this about.

This kind of book is out of date the day it is printed, so prolific are the investigators, but it is a useful guide to present-day knowledge.

Recent Advances in Cerebral Palsy. Edited by Ronald S. Illingworth. (Pp. x+ 389; 136 figures. 50*s*.) London: J. & A. Churchill. 1958.

Public interest in, and sympathy for, children who are crippled by various motor disorders has led to a special interest being taken in what are generally called "spastics". Many of these children are of course mentally defective and the separation of those who have severe motor disorder into a group to be given special attention may at times become unreasonable.

Professor Illingworth has, however, concentrated on those who are palsied, and from this point of view his book is essentially practical and simple, so that it may be referred to with advantage by the various medical auxiliaries who deal with these children. Various types of physiotherapy are described but the terms used often mean little to the uninitiated; so perhaps success depends more on the personality of the therapist than on the method used.

It is, however, disappointing that the scientific aspects of this difficult subject are neglected. Thus the fundamental importance of embryological and neurophysiological studies are ignored, and indeed both the neurological and pathological findings receive only scant and superficial consideration.

A Primer of Cerebral Palsy. By Joseph D. Russ and Hyman R. Soboloff. (Pp. viii + 77; 16 figures. 30*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

Public sympathy for children with cerebral palsy has provoked the medical profession to try and do something about the problem. The authors of this small book are closely associated with cerebral palsy centres in the U.S.A. and it is somewhat startling to read of the large variety of specialists concerned with these unfortunate cripples. Thus there is an orthopaedist, paediatrician, physiatrist, neurologist, psychiatrist, psychologist, ophthalmologist, otolaryngologist, and dentist. As regards treatment there is a physical therapist, occupational therapist, speech therapist, nursery school teacher, special education teacher, vocational rehabilitation worker, medical social worker, public health nurse, and the administrator. It is remarkable that the little patients progress favourably under the scrutiny of such a formidable gathering!

Lectures on Epilepsy. Edited by A. M. Lorentz de Haas. (Pp. viii + 172; 13 figures. 24*s*.) London: D. Van Nostrand Company Ltd. 1959.

These lectures are concerned with reports from research workers in France, Norway, Switzerland, and the Netherlands, and it is clear that some refreshing approaches to the problem of epilepsy are under active study. Thus Professor M. David and Dr. Michelle B. Dell (Paris) write " . . . with the exception of such cases as involve an unmistakable cortical lesion, the surgical approach (to epilepsy) should be based not so much on the suppression of specific lesions as on the interruption of a circuit or the alteration of a system. The conception of a functional type of neurosurgery, therefore, would seem to prevail over that of a specific lesional type of surgery."

Epilepsy Handbook. By Frederick A. Gibbs and Frederick W. Stamps. (Pp. ix + 101; 8 figures, 3 tables. 36*s*.) Oxford: Blackwell Scientific Publications. 1958.

This small book sets out to be a compact practical compendium of useful knowledge about epilepsy, and on the whole it succeeds. The chapters on treatment and general management are excellent. The chapters on causes and types of epilepsy reflect the current differences of opinion on classification. The authors consider epilepsy as "what the brain does when it is slightly injured" but also appear to consider it a disease *sui generis*. These two views at times make uneasy bedfellows: especially as the authors consider the constitutional factor as relatively unimportant. Further difficulties arise from a slight tendency to force clinical classification to fit E.E.G. findings. Thus post-alcoholic fits and narcolepsy/cataplexy are regarded as non-epileptic, whereas febrile convulsions and attacks of

dizziness and pain, or uncontrollable rage associated with E.E.G. changes, are considered epileptic. The latter are labelled thalamic and hypothalamic epilepsy (there is no mention of Gower's vasovagal attacks). Nevertheless the descriptions of various clinical forms of epilepsy are clear and concise and where appropriate accompanying E.E.G. abnormalities are well illustrated.

The Physical Foundation of Biology. By Walter M. Elsasser. (Pp. 219; 16 figures. 30*s*.) London: Pergamon Press. 1958.

This book is written by the Professor of Physics in the University of California. He introduces himself as "a theoretical physicist fairly familiar by long practice with various aspects of biology". The first two-thirds of the book are an exposition of three physical subjects in their relation to biological phenomena. He discusses in turn the theory of automata, *i.e.*, computers, information theory, and the theory of microscopic measurement, and the description of these is clear, lucid and non-mathematical. The rather difficult concepts underlying information theory are discussed, and analogies and comparisons are made with biological systems. A section of particular interest to neurologists is that on pulse codes in which the author comes to the conclusion that the analogue character of cerebral operation has not always had the attention it deserves.

He then begins to draw away from purely mechanistic ideas and in the chapter on storage and memory writes:

> "There is no anatomical evidence for a storage organ." . . . "Brain physiology has not brought to light any evidence for the existence of the highly complicated special scanning devices. . . . The apparently complete absence of a limit to the amount of information that can thus be maintained . . . by the human brain."

Here a larger acquaintance with clinical neurology might have made the author's task easier. A study of clinical conditions involving defects in memory indeed suggest that there is no evidence for a storage *organ*, but make it seem possible that the mechanisms of both analysis and storage are anatomically so close that they cannot easily be separated by the lesions of disease, or experiment. Defects in visualization are of special interest here. On purely physical grounds the postulation of biotonic laws not deducible from physics is made. This view is contrary in many ways to that taken by Schrödinger in "What is Life".

In general, however, this is an informative, provocative, and stimulating book of considerable importance to neurologists and psychologists. There is an excellent summary of the chapters with page references at the end of the book which makes the sequence of arguments easier to follow.

Neurological and Psychological Deficits of Asphyxia Neonatorum. Edited by William F. Windle. (Pp. xiv + 336; 83 figures. 60*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

This book reports the papers given at a conference held in September, 1956, which was sponsored by various institutes and associations, including the United Cerebral Palsy Association. The frustrations and difficulties of the subject are well illustrated by these contributions, but the developing work on experimental animals is reported by several workers and holds promise for the future.

The Psychiatric Hospital as a Small Society. By William Caudill. (Pp. xxii + 406: illustrated. 52*s*.) Harvard University Press (London: Oxford University Press). 1958.

The author of this book is a social anthropologist who spent several months as an observer at a small psychiatric hospital in America. He spent several months on the wards, and attended the daily conferences of doctors, nurses, and ancillary staff. He also devised a projection test of a series of pictures of situations in the hospital which he presented to patients and to members of the staff.

He demonstrates the conflict between therapeutic and administrative requirements in the handling of patients, and how differences of opinion between senior and junior medical staff influence the progress of treatment of a patient. His analysis of the daily administrative conferences shows the interplay between the individual doctors, and between the different hierarchical groups, senior doctors, junior doctors, nurses, and so on.

There can be little doubt that far more happens when a patient enters a psychiatric hospital than that he is given some specific treatment and, perhaps, improves. The nature of the treatment often depends upon irrational factors, and whether or not the patient improves depends at least to some extent upon the relationships between the various members of the staff and the other patients as well as upon the specific treatment he receives. These are all factors which are little understood but are of considerable importance. Although this study is applicable to an American hospital where conditions are very different from those in this country, there are many points of interest in this stimulating book.

Attempted Suicide: Its Social Significance and Effects Vol. 4 (Maudsley Monographs). By E. Stengel and Nancy G. Cook. (Pp. 136. 25*s*.) London: Chapman and Hall (for the Institute of Psychiatry). 1958.

This book is the fourth of the Maudsley Monographs. There is a review of the present state of research into suicide and the difficulties inherent in any such research. Much factual evidence is then given about five groups of attempted suicides and one group of successful suicides, frequently in tabular form. Such a presentation makes for very dull reading unless it is relieved by discussion of the significance of the facts. There is, in fact, a paucity of discussion and little integration of the findings of the various groups.

The main conclusion of the authors is that attempted suicide is not the same as unsuccessful suicide but is a final appeal to the community for help. This is a somewhat naïve conclusion and the evidence for it, amongst such a welter of data, is anecdotal rather than statistical.

If a reprint should be called for it is hoped that the many errors in the bibliography will be corrected.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books received.)

Psychiatry in the British Army in the Second World War. By Robert H. Ahrenfeldt. (Pp. xv + 312. 35*s*.) London: Routledge & Kegan Paul. 1958.

Psychosomatic Correlation in its Biochemical Aspect [Lecture]. By P. Puig Muset. IV International Congress of Psychotherapy. (48 typewritten pages + references). Barcelona: P. Puig Muset. 1958.

Minds Matter: A New Approach to Mental Health. By Beryl P. Cooper. (Pp. 62. 2*s*. 6*d*.) London: Conservative Political Centre. 1958.

Mental Deficiency: The Changing Outlook. Edited by Ann M. Clarke and A. D. B. Clarke. (Pp. xvi + 513; 4 figures, 26 tables. 45*s*.) London: Methuen. 1958.

Mental Health Aspects of the Peaceful Uses of Atomic Energy. *Wld. Hlth. Org. tech. Rep. Ser. No.* 151. (Pp. 53. 3*s*. 6*d*.) London: H.M.S.O.; Geneva: World Health Organization. 1958.

Métabolisme de L'Eau dans les Traumatismes du Crâne. By D. Petit-Dutailis and E. Bernard-Weil. (Pp. 108; 10 figures. Fr. fr. 1,400.-.) Paris: Masson. 1958.

Adénomes Hypophysaires. By Gérard Guiot and collaborators. (Pp. 276; 118 figures. Fr. fr. 3,800.-.) Paris: Masson. 1958.

L'Angiographie Cérébrale. By Joël Bonnal and Jacques Legré; Foreword by Prof. J.-E. Paillas. (Pp. 254; 223 figures.) Paris: Masson. 1958.

Mehrdimensionale Diagnostik und Therapie. By Ernst Kretschmer. (Pp. viii + 308; 7 figures. DM 36.-.) Stuttgart: Georg Thieme. 1958.

Biochemistry and the Central Nervous System, 2nd ed. By Henry McIlwain. (Pp. vii + 288; illustrated. 45*s*.) London: J. & A. Churchill. 1959.

Traumatismos Vertebromedulares Cervicais com perturbacoes Nervosas. By A. Ferreira Alves and C. Andrade. (Pp. 109; 50 figures.) Porto: Maranus. 1958.

Grosse Nervenärzte, Vol. 2. Edited by Kurt Kolle. (Pp. x + 252; 211 photographs. DM. 29.40.) Stuttgart: Georg Thieme. 1959.

Sensorische Aphasien und Amusien auf myeloarchitektonischer Grundlage. By K. Kleist. (Pp. viii + 45; 47 figures. DM 16.80.) Stuttgart: Georg Thieme. 1959.

Mental Disorders, 5th ed. By W. S. Dawson. (Pp. 68. 2*s*. 6*d*.) Edinburgh and London: E. & S. Livingstone. 1958.

Psychological Stress. By Irving L. Janis. (Pp. xiv + 439. 56*s*.) London: Chapman & Hall; New York: John Wiley. 1958.

Personality Patterns of Psychiatrists, Vols. 1 and 2. By Robert R. Holt and Lester Luborsky; Foreword by Robert P. Knight. (Pp. xiv + 386. $7.50, and pp. xiv + 400. $4.00, respectively). New York: Basic Books. 1958.

Temporal Lobe Epilepsy. A colloquium presented under the auspices of The National Institutes of Health. Edited by Maitland Baldwin and Pearce Bailey. (Pp. xiii + 581; illustrated. £5 17*s*. 6*d*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

Physiologie du Système Nerveux Central, 3rd ed., entirely revised. By Georges Morin. (Pp. 396; 104 figures. Fr. fr. 3,400.-.) Paris: Masson. 1958.

L'Exploration Chirurgicale Stéréotaxique du Lobe Temporal dans L'Epilepsie Temporale. By J. Talairach, P. Tournoux, and M. David. (Pp. 136; 29 figures, 56 plates. Fr. fr. 3,150.-.) Paris: Masson. 1958.

Chronic Subdural Hematoma: With Particular Reference to the Diagnosis. A Clinical, Roentgenological and Electroencephalographical Study. By Ragnar Nordlie. (Pp. 164; 24 figures.) Oslo: Johan Grundt Tanum Forlag. 1958.

Topométrie Cranio-Encéphalique chez L'Homme. By A. Delmas and B. Pertuiset in collaboration with M. H. Pineau. (Pp. 436; heavily illustrated. £14.) Paris: Masson; Oxford: Blackwell Scientific Publications; Toronto: Ryerson Press. 1959.

Der Psychiater. By Kurt Kolle. (Pp. 57. DM 5.40.) Stuttgart: Georg Thieme. 1959.

A Textbook in Rorschach Test Diagnosis. By Edward Bohm; translated by Anne and Samuel Beck. (Pp. xi + 322. $7.75.) New York and London: Grune & Stratton. 1958.

Personality Change and Development As Measured by the Projective Techniques. By Molly Harrower. (Pp. 383; heavily illustrated. $10.00) New York and London: Grune & Stratton. 1958.

Sequelae of Primary Aseptic Meningo-encephalitis. By Ragnar Müller, Ingvar Nylander, Lars-Erik Larsson, and Lennart Widen. (Pp. 115; illustrated.) Copenhagen: Ejnar Munksgaard. 1958.

The Nature of Experience. Riddell Memorial Lectures, 30th Series. By Sir Russell Brain. (Pp. 73. 8*s*. 6*d*.) London: Oxford University Press. 1959.

Medulloblastoma. By Benjamin L. Crue, Jr. (Pp. x + 206; 16 figures. 43*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

Psychiatric Congress

A Czechoslovak psychiatric congress with international participation will take place at Jesenik Spa, Grafenberg, from September 7 to 11, 1959. Further information may be obtained from Dr. E. Wolf, Secretariat of the Psychiatric Congress, Ke Karlovu 11, Praha 2, Czechoslovakia.

Ninth Annual Instrument Symposium

The Ninth Annual Instrument Symposium and Research Equipment Exhibit will be held from September 28 to October 1, 1959, at the National Institutes of Health, Bethesda, Maryland. Further information may be obtained from James B. Davies, National Institutes of Health, Public Health Service, Bethesda 14, Maryland.

Scandinavian Society of Neurosurgery

The 14th annual meeting of the Scandinavian Society of Neurosurgery (Nordisk Neurokirurgisk Forening), will take place at Södersjukhuset, Stockholm, Sweden, on September 4 and 5, 1959. Further information may be obtained from Docent R. Frykholm, M.D., Södersjukhuset, Stockholm.

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MEMORIES OF HUGH CAIRNS*

BY

SIR GEOFFREY JEFFERSON

Hugh Cairns was born at Port Pirie in South Australia on June 26, 1896. That is the starting point, but some enrichment should come from a sketch of his early days and his Australian background. To be born of sound, if humble, stock under the high and wide Australian skies is as fine a beginning as a man could desire. His father, William Cairns, threatened with tuberculosis, had sailed out from Scotland on medical advice. At Port Pirie he had found work in timber construction for the loading of ships, for this was the port of shipment from the smelting plant of the great Broken Hill Proprietory, Australia's chief up-country mining area and today its largest and richest company. In Broken Hill, silver, lead, and other metals had been found in quantity. Hugh went to school at Port Pirie, transferring to the Riverton High School when his parents moved away to this quiet little place of some 600 or 700 people. It lies in good agricultural farming land and sheep country. Many of Australia's best vineyards are not far away, and it is a pity that we rarely see their products. There Hugh's parents established themselves, his mother in particular being still remembered as a very kind woman to whom all went for advice, She had natural talents and a zest for life; she was one to whom everyone in the village went with their troubles. Perhaps from her he inherited his love of music, which she taught, but there was also his father with his violin playing. Hugh inherited something else from his father, a perfectionist trait in manual skills. The son was fortunate to have fused into his character so much of the best qualities of his parents. I have had the pleasure of visiting Riverton, a quiet place indeed, basking and often baking in the brilliant sun and heat of South Australia. I saw the little primary school and met, by request, two or three people who had been Hugh's school fellows. It is a mixed school now, as in Hugh's day, boys and girls in one room, a practice common enough in small schools in our own country. A boy who made stupid answers was put back to sit with the girls. This was not Hugh's fate, because from early days, they still remember, he learned so fast that he outshone his companions. There is a story current at Riverton that a visitor who had asked him, as, aged about 4 or 5, he sat on the floor playing, what he wished to be, received the reply, "the greatest doctor on earth!" Only just credible, I suppose. The child went far on the way to that impossible goal. It was not long before

Col., later Brig., Sir Hugh Cairns, K.B.E.

*The first Sir Hugh Cairns Memorial Lecture delivered at the London Hospital in October, 1958.

Hugh won a bursary that took him 60 miles to the Adelaide High School. This is a fine school by any standards, as so many Australian schools are, finely rebuilt since Cairns' day. In conversation with his old headmaster, Mr. West, I found that he was deeply impressed still by his memories of the boy. "A bright, frank, and candid boy—always popular but never seeking to be," he said of him, "always top of his class and finally top of the school." No one, I venture to say, will deny that this was a wonderfully accurate forecast of the character of the man. Winning an exhibition he moved on to Adelaide University where he continued his unbroken story of success. There he met Leonard Lindon who, as another oarsman, Rhodes Scholar, and eventual neurosurgeon, became one of his closest friends. They had many qualities in common. Hugh Cairns was not noted, it seems, for athletic prowess until he took up rowing at the University. Soon he was in the Adelaide University crew as he was again at Oxford, gaining his "Blue" in 1920. Rowing men rarely excel at ball games and though Hugh Cairns was interested in all sport he by no means allowed that interest to encroach on his work. Work dominated his life from the earliest days; it was dogged that did it, he was not to be distracted from the task in hand. On leaving Oxford he abandoned rowing to work for his F.R.C.S., the aim of all good Australians with surgical ambitions and a worthy one. He and Lindon roomed in the same house as Archie Malloch, the young Canadian who had watched at Osler's bedside and became eventually Librarian to the New York Academy of Medicine; they burned his gas-fire far into the night, having no money for their own.

The high spot in his life so far had been his acquisition of a Rhodes Scholarship in 1919. Balliol was his College, and he could have had no better. He gave it all his loyalty and admiration (in 1937 Balliol repaid him by making him a Fellow). Before this he had had two periods with the army in the First World War, was invalided back to Adelaide from Lemnos with typhoid, there to finish his medical studies and return at once to France to an English battalion until the war's end.

Hugh Cairns went to the London Hospital after having a resident post at the Radcliffe Infirmary. He was house surgeon to Henry Souttar (1921) and house physician to Sir Robert Hutchison in the same year. He had already been assistant in pathology under Professor Turnbull where he began the work on tumours of the testis that he presented as his address as Hunterian Professor at the Royal College of Surgeons in 1925. Turnbull, whom he greatly admired, certainly implanted in Hugh a life-long interest in pathology. By this time he was assistant on the Surgical Unit under (Sir) Henry Souttar, Director of the Surgical Unit. At the suggestion of Alan Gregg, from that time on his friend and helper, and fired by his reading of Harvey Cushing's writings, he applied successfully for a Rockefeller Travelling Scholarship and went to the Peter Bent Brigham Hospital for 12 months in September, 1926, shortly after appointment to the honorary staff of the London Hospital (June 2, 1926—full surgeon June 7, 1933). From that time on his future was certain.

Stimulated by Cushing's example by what he had learned at first hand and by Cushing's advice he had decided to devote his life to neurological surgery as a specialty. Many wagged their beards in dismay because no surgeon in London had ever thought that he could make a living out of so recondite a pursuit—nobody, that is, since Victor Horsley, and he had done a little general surgery. Much wiser, it was thought, would it be to take neurosurgery as a sort of dilettante hobby, an ornamental sideline to bread-and-butter general surgery in the way that Percy Sargent was so successfully doing. Cairns was nothing if not stubborn and, it must be said, courageous. Aided by a grant from the Rockefeller Foundation arranged for him by Alan Gregg, he thought that he could get by if he lived quietly. There were hardships as there were for all ambitious young men without capital in those times. The project could not have succeeded except with the collusion and help of his wife, Barbara Smith, the beautiful youngest daughter of the Master of Balliol. By the happy circumstance of his marriage Hugh had forged another link binding him to Oxford. Fortune had certainly smiled in other ways as well on this vigorous and friendly young Australian with the charming manners, for there was nothing brash or raw about Hugh—nothing, that is, if he was getting his own way! Rarely did he fail to do so, for everything seemed to come to him of its own accord.

The year of his return from Boston saw the start of his efforts to found a neurosurgical department to pair with the medical neurology of George Riddoch and Russell Brain. This had meant a breakaway from Souttar and such neurosurgery as was already in being. Cairns thought this break unavoidable. He wished to apply the special techniques, the team work, and ways of thinking that he had learned with Harvey Cushing and he knew that he could do so only if he were in control and independent. Cairns felt badly about the break because Souttar had been nothing but kind and helpful to him. In his last illness Hugh Cairns told me that it still worried him that he had hurt Souttar's feelings. As a junior surgeon there were

difficulties in establishing something different from the traditional teaching hospital unit. I know this because I was facing the same problems at the same time but with more encouragement from colleagues. It was our common enterprise that bound Hugh Cairns and me together at an important time—that and perhaps a mutual liking. (When I read again, as I have been doing lately, his letters to me from 1929 onwards, Hugh's personality, his generosity, come back to me as if he were alive, as if I had only to reach out for the telephone and I could speak to him.) The ideal we shared was of a self-contained unit with the ambition to raise the work done in it to the top level of international ranking. This did not come about overnight, for either of us. It was 1932 before these units were firmly established: in Manchester, my own with Harry Platt's in orthopaedics in our hospital epitomized a veritable revolution in the finding of a sufficiency of beds for specialties in a teaching hospital. Hugh's unit at the London Hospital was not officially established until 1934 but was no more than a formal acknowledgement of an established fact.

In 1930 we find him Secretary to the Section of Surgery at the B.M.A. Meeting in Canada. Cairns had already won a considerable reputation and he was shortly joined at the London by overseas trainees—Frank Morgan (Melbourne), Hugo Krayenbühl (Zurich), Almeida Lima (Lisbon), and Obrador (Madrid) amongst others—all men of the highest quality who have since made great names in neurosurgery. Douglas Northfield came to join Cairns in 1934 when his unit was complete and remained his staunch and intelligent aide, to become his admirable and wise successor.

Following the lead of Cushing and other Americans, he made his private patients come to consult him in the rather poky little room at the London Hospital that was all that he had of his own. It was a fault of our hospital construction that there was no place for any of the honorary staff to sit and work and write. There were the wards and the operating theatre and somewhere for the surgeon to hang his hat while he operated or did ward rounds—no more. That used to madden me—as it did Hugh Cairns. But anyone who wanted more was thought to be an odd sort of fish. If he were a neurosurgeon too he was probably crazy. Nowadays only the elder staff members remember that the idea of dealing with private patients at teaching hospitals was not only a new one 30 years ago but one that did not commend universal approval. That state of affairs has now been remedied as everyone knows. It came about at the London Hospital in 1936, and Cairns had been on the Committee forwarding the change. What was equally bad was that facilities for clinical research were virtually non-existent and (what was equally bad) many universities had either no or inadequate facilities for survival experiments on animals.

Reports on Cushing's Work

The publication by the Medical Research Council in 1929 of Cairns' special report had brought him at once into the public eye. It was an account of the work done in the 12 months, September, 1926-27, when he was working as one of Harvey Cushing's assistants at the Peter Bent Brigham Hospital in Boston. Previously, in reports by Cushing himself, whether in his books or in his many papers and in those of his asistants, the objectives had been limited to descriptions of some or other neuropathological or clinical or surgical subject. Cairns' report was different. It had the great advantage that it covered the whole field, giving a global view of a year's work in intracranial tumour surgery by the master surgeon of the day. Although the material was Cushing's there was a great deal of Cairns in it. It was in fact so cleverly composed and illustrated by the occasional case history that it made first-rate reading and time has not diminished its interest. Of the 369 cases admitted to the Brigham during Cairns' stay, 157 had tumours verified histologically and of those the 135 survivors proved the material for Cairns' later follow-up review in 1936. To that I shall refer in a moment. The clinical accounts show all the care that was to mark Cairns' future work. He brought back to this country a characteristic of Cushing, the continual appraisal and periodic publication of his surgical mortality and something else—the forging of bonds between the patient and his surgeon so that after-histories were known. This had been a necessary and indeed a basic feature of Cushing's work since he was determined to establish the life history, the natural history of the so various tumours. The other thing that emerged was the importance of study of the visual fields applied to most neurological and all neurosurgical cases. Field studies were no new thing to us in Britain but Cushing was the first surgeon to make great use of them. The lucky chance of the coming of C. B. Walker to work with Cushing led to the introduction of quantitative perimetry. It was an ironical fact that Cushing's earlier erroneous belief that interlacement of the colour fields was a reliable sign of brain tumour led him to operate on General Leonard Wood's meningioma, an operation the success of which, he told me, he thought had played a considerable part in his invitation to leave the Johns Hopkins Hospital for Harvard. Cairns in his report discussed ventriculography. It had been used in no more than 37 of the 369 cases and

was the cause of death in two and of grave symptoms in a third. Cushing had been first hostile to and then niggardly in the use of pneumography, not merely because it came from Dandy but because he believed that it was more dangerous than Dandy allowed and there he was right. Glancing over the material for that year when Cairns was there, we see that there were 61 patients with gliomas operated upon, of whom 11 died (18%), 29 patients with pituitary adenomas of whom one died (3·4%), all but two operated on by the trans-sphenoidal route. and 28 patients with meningiomas with five deaths (17·8% mortality). To have seen all those cases so skilfully handled, to have been one of a team of devoted young men, to have watched the tumour types so expertly differentiated by Percival Bailey, and to have worked in a clinic where discipline was so high and where hours of work to the point of exhaustion were the rule—all this was a wonderful experience. (Norman Dott had been through it two years earlier.)

This report made it clear that a new figure had emerged on the London stage. Patients began to come to him not only from the staff of his own hospital; soon he had accepted an appointment to the Maida Vale Hospital (1931) and to Queen Square in 1935. In no time, as it seems looking back on it, he was reading papers on subjects that remained his favourites—brain abscess and injuries of the dura by fractures involving the paranasal sinuses. But by the year 1937 he was able to read a paper in Zurich describing his own tumour work during the 12 months of 1936 which almost matches what he had seen in Boston exactly 10 years earlier. He had had 120 verified tumours: 47 gliomas with a 12·7% mortality, 21 meningiomas with two deaths (9·5% mortality), eight acoustic neuromas, and seven angioblastic tumours, both with no deaths. The only score on which Cushing was much ahead was that of the pituitary, for Cairns had only 10 cases and three patients died—an unlucky run.

To revert to what I called a pet subject of Cairns, brain abscess. In 1930 he took part in the discussion by the otologists on this subject. Heinrich von Neumann of Vienna, then one of the most famous in his field, spoke of the cases that he had collected from the literature. Of 387 patients with temporal lobe abscesses, 61% had died and 88% of 124 patients with cerebellar abscesses. Von Neumann himself had had two recoveries in 27 cases. When Cairns came to speak he was emphatic on the need for better and more studious clinical examinations of these cases. Too many of the 200 patients with brain abscesses found in the post-mortem room since Professor Turnbull had began to keep accurate records at the London Hospital in 1908 had died in medical beds after admission in coma or with wrong diagnoses. He gave excellent and much needed advice on needling the brain and on the deductions that could be drawn from what one saw through a large enough burr hole. The results of the surgery of brain abscess did not immediately improve. Three years later he reported with Charles Donald his own figures. He had had 10 recoveries in 23 patients. We were, nevertheless, all set for the revolution unparalled elsewhere in the body which did eventually come from penicillin and the other antibiotics and bacteriostatics—a work in which the Oxford School, first under Cairns then under Pennybacker, has excelled.

I must pass over with little more than a mention some papers such as that on head injury (with Russell Brain, 1928), on the treatment of spinal ependymomas (with George Riddoch, 1931), on the treatment of glioblastomas with radium (with Stanford Cade, 1931), his experiments with John Fulton on the effects of radon on the spinal cord (1930), and the very carefully described and cautiously treated case of pinealoma (with Wilfred Harris, 1932).

Cairns never lost the enthusiasm for pathology which had brought him originally to Turnbull's laboratory and finding there that remarkable person, Dorothy Russell, seized on to her to give him the sort of help that Cushing had had from Percival Bailey. Knowing that she was interested and could be more so in the structure of brain tumours he put her up for a Rockefeller Travelling Scholarship and sent her off to study in the States. Thus began a most valuable partnership, only broken when she declined to accompany him when he moved to Oxford, a refusal which astonished him. But those privileged to know Professor Russell will readily credit her with having a mind and purpose of her own. The fortunes of war took her in good time willy-nilly to Oxford but she did not stay. Hortega was already a bird of passage there. However, the Cairns-Russell partnership was a vitally important factor in Hugh Cairns' development and in the success of the London Hospital department. They wrote together two important papers on the seeding through the subarachnoid fluid pathways of gliomas, not only malignant but benign, papers marked by scrupulous technique. The older members of the Society of British Neurological Surgeons perhaps remember a joint paper given by Hugh Cairns and Dorothy Russell on the way in which different sorts of stains would bring out important variations in the histological appearances of brain tumours. Professor Russell's work on the tissue culture of intracranial tumours stemmed from those beginnings.

In 1935 Cairns went back, this time to New Haven

because Harvey Cushing was there now as Professor of Neurology at Yale and where Dr. Louise Eisenhardt had set up the Brain Tumour Registry. Cairns' object was to find out not only who of the patients operated upon by Cushing at the Brigham in 1927-28 were still alive but also to enquire into the usefulness of the lives that they had led. Cushing was delighted to have him back for he had been fond of Hugh, he admired him and was proud of him. Above all it was a matter for the greatest satisfaction that he had in him a really flourishing, respected, and well-thought of pupil in London. Too many London neurologists had been unfriendly to Cushing, had belittled his achievements. Jibes at his slow, careful Halsted method of operating were overheard by visitors from the U.S.A. and reported back home. Cushing was too sure of himself to care greatly but it was a good reply to get British disciples. Dott and Cairns were outstanding examples. Hugh Cairns' report on his follow-up was published in 1936. Of the 135 patients who had survived operation he found that 72 had died since, 63 were alive seven to nine years afterwards, and of those the best performance had been given, as we should expect, by those with acoustic neurinomas, pituitary tumours, and the menigiomas. Three of four cases of cerebellar astrocytoma were alive, and four of 15 cases of hemispheral astrocytoma. The average survival of patients with gliobastoma had been six and a half months, the longest 14 months. We know now that Cushing himself had spent too much time on those malignant gliomas but so had many of us until angiography came along mercifully to release us from that hopeless burden.

This survey by Cairns is a model of its kind; his discussion of what constitutes usefulness in life shows that knowledge of psychology which was to emerge in a later period of his work. While on this visit he wrote to Barbara that he was formulating a plan in his mind for something big and new at Oxford. We know now what that was.

An important discovery that belongs to the 1930s was the description with C. S. Hallpike of the temporal bones from two patients who had died from intracerebellar clots after eighth nerve sections for the Ménière syndrome. Cairns had kept the four temporal bones in the hope of salvaging something important from disaster. After six months' thought and enquiry as to whose would be the safest hands to receive this precious material, he acted on Turnbull's advice and gave them to Hallpike, then at the Ferens Institute. Hallpike has told me how very carefully he was cross-examined and how cagely he was looked over before Cairns thought it safe to put the bones into his hands for histology, with what eventual result everybody knows (1938).

Hugh Cairns had now been established in London for 10 years. By the honesty of his opinions, by his very likeableness, and by his unquestioned skill he had built up not only a first-class neurosurgical department at the London Hospital but he had acquired a busy private practice, one more time-consuming, more demanding than he found convenient or desirable. With his heart really in the London Hospital but his livelihood in the nursing homes of the Harley and Wimpole Streets area he was finding it difficult to live up to the ideals of perfection that he had long ago set himself. He was still the only whole-time neurological surgeon in London and even had he not been, who can doubt that his popularity would have been as great and his dilemma no less. He had been appointed to the National Hospital in 1935 but he operated on only one case there; he already had other fish to fry. He and I had worked hard on Alan Gregg to get the Rockefeller Foundation to give a large sum to that hospital for the creation of adequate surgical accommodation and for new research laboratories. We worked together again on the plans for the new block but on the subject of his own future in this hospital he was sometimes sure, sometimes vague, and it was not long before the first hints of something likely to happen elsewhere were detectable in the air.

The Oxford Dream

At the B.M.A's 104th Annual Meeting, which took place at Oxford in July, 1936, Hugh was evidently excited about something. He said when inviting me to a small dinner in New College, at which Lord Nuffield and Farquhar Buzzard were to be present with others, that he was bursting to tell me what was on foot but could not yet. The Presidential address, which had been given by Sir E. Farquhar Buzzard, then Regius Professor of Medicine, gave a likely clue. It was inadequately entitled "And the future". In it the President sketched a future in which the young doctor would have ample opportunity for research, where some chosen men could lead departments of medicine, surgery, and obstetrics in which the care of patients and research would be almost their only duties. They were to be fully and adequately paid. He thought that Oxford was the right place for this because of its ideal atmosphere for the advancement of knowledge and because of the excellence of the departments ancillary to clinical study. This ideal school would be in close touch with physiologists, biochemists, pathologists, pharmacologists, and radiologists. Here would be the place for the training of those fitted by ambition and ability to find a career in research. Their clinical teachers could give them all their time if they were freed from

the heavy burden of teaching medical students.

Farquhar Buzzard went on to remark that the better educated a man is the more time he needs—time to work, time to think. Maybe it was, he added, no more than an ambitious dream. Although Farquhar Buzzard's interest in medical education was well known, he was conservative in his outlook but shrewd and a man of great influence in the University's affairs. His knowledge of procedure made him the ideal person to present to the University's officers this new plan. It will be no surprise to discover that the propositions made in his Presidential address were not entirely original. The ideas had been put crisply and in detail to him by Hugh Cairns, but those who remember the circumstances say that it would be unfair to Buzzard to speak of him only as a mouthpiece. Buzzard realized that in Cairns he had a man with an energy and a driving force that perhaps he lacked himself so he joined wholeheartedly in collaboration in a scheme of which he himself heartily approved. Of the magnitude of Cairns' part there can be no doubt. He had started to draw up plans some time in 1934.

Sir Arthur Ellis, who eventually succeeded Buzzard as Regius Professor, has told me of private meetings at Cairns' house at 24, St. John's Wood Park, at which the Oxford Vice Chancellor, A. D. (later Lord) Lindsay, (Sir) Douglas Veale, the University Registrar, and himself were present. There were several such meetings during which the scheme was thrashed out with Cairns leading, pleading, and convincing. Late in 1934 or early 1935 Cairns sent to Farquhar Buzzard a "Memorandum to the Regius Professor of Medicine on the desirability of establishing a complete School of Clinical Medicine at Oxford". The arguments were roughly those that Buzzard himself used in the Presidential address referred to. They were these: that although the British schools of physiology had continued pre-eminent, above all those at Oxford and at Cambridge, in the clinical fields we had contributed remarkably little outside of neurology and cardiology. What fundamental research we had on our credit side had been applied more energetically abroad than here at home. Cairns went on to say that Oxford was the place above all others in which to found a new school. It had no large commitments to undergraduates whose yearly entry could be limited to 20 at most, all carefully selected men. The postgraduates, who would come for six to eight years' training and research, could be hand-picked from countries all over the world. Cairns estimated that £600,000 to £1,000,000 would be required to endow a sufficiency of fully salaried posts. He added that the present Regius Professor (Farquhar Buzzard) had great influence outside the University as well as within it. He would be just the man to sponsor the scheme. A second document (March, 1936) is firmer in tone, as if he had had enough encouragement and knew that he had at least strong moral support for his plan. It is headed "Second Memorandum from Mr. Cairns to the Regius Professor etc.", is 39 pages long, and restates the arguments for the foundation of a research school with estimates of capital cost and annual expenditure. This was drafted with the help of Lady Cairns and a friend as secretary. The salaries for these people in their sixth, seventh, and eighth years would be £200 p.a. which was about the same as the Johns Hopkins level. There are estimates for the already existing Nuffield Institute of Clinical Research (in Professor Gunn's charge), medicine, pathology, pathological biochemistry, surgery (slightly the most expensive item), gynaecology and obstetrics, paediatrics, radiology. Anaesthesia was not mentioned. The reason why this last fact is brought up will appear shortly. Cairns did not know at that date where the money could be found; he wondered if the Government might considerably help. He said that if half the needful sum could be got, pious benefactors would emulate William of Wykeham, Radcliffe, and William of Waynflete in providing the balance. It is noteworthy that in this early plan the heads of all the departments were called director or reader, the only professor mentioned was the Regius who was to be in clinical charge of the medical unit. Oxford was not yet asked to accept the innovation of multiple clinical professorships.

Sir Arthur Ellis says that when bidding good-bye to Lord Nuffield, who had been Buzzard's guest of honour at the 1936 B.M.A. banquet, Buzzard slipped the Cairns document into Nuffield's pocket saying, "Read this when you get home". And now Lady Cairns tells me of something even more cogent, more perpendicular to our story.

Mrs. Smith, widow of the Master of Balliol and a "grande dame" of Oxford, introduced her son-in-law to Lord Nuffield at the B.M.A. reception in Christ Church. Cairns obtained an interview for the following Sunday. Apparently Lord Nuffield sat and listened whilst his visitor developed the scheme, we can be sure with great power, for an hour. Lord Nuffield said very little but at the close told Cairns that he would do the whole thing himself. He had sat weighing Cairns up and decided that he was a man with "fire in his belly". Naturally Hugh was wild with excitement. Lord Nuffield tells me that he himself had had it in his mind for some time to do something for Oxford medicine. No doubt willing donor and convincing supplicant met

at this meeting. Lord Nuffield had already helped the Orthopaedic Hospital at Headington generously, even more generously he had bought the Radcliffe Observatory site and started the unit which became under Professor James Gunn the Nuffield Institute for Medical Research.

The Nuffield Professors

In October, 1936, Lord Nuffield announced his intention of giving £1,250,000 for the creation of a medical research school. This was tremendous news. Hugh wrote to me soon after in reply to a letter congratulating him on his accomplishment for I had guessed his part in it. "I have been itching to talk to you about Oxford ever since the night of that dinner at New College. *You* can imagine what a strain it has been not to talk. . . ."

In Lord Nuffield's letter to the Vice-Chancellor, remark is made of Farguhar Buzzard's phrase "an ambitious dream". Lord Nuffield continued:

> "It would be a great pleasure to me to help in giving reality to this dream in a city where there are already hospitals with which I have the satisfaction of being closely associated and in a University of which I am proud to be an honorary graduate and where, though on a small scale, is already an Institute for Medical Research."

He announced that he wished for the foundation of a trust to administer the fund, and of that Mr. (later Sir) William M. Goodenough was later made chairman. Goodenough was already treasurer of the Radcliffe Infirmary and Chairman of the Oxford County Council. He was an influential man and so he remained, as we all know, for did he not become through his special committee the arbiter of all our fortunes?

At the special meeting of Congregation at Oxford, convened in Lord Nuffield's presence to carry a decree to set up an organization to establish the new school, Lord Nuffield stood up to speak and said that he had been thinking things over as he listened and decided that the sum he had given was not enough and that he had decided to increase his gift to two million pounds to be applied to the creation of four professorships—medicine, surgery, obstetrics, and anaesthesia. On the last named he was adamant. The University, so Professor Macintosh tells me, boggled over the chair in anaesthetics. Finding that Lord Nuffield was determined that it was a subject crying for research, so that it was all or nothing, the University gave in. Lord Nuffield followed up in October, 1937, with a further £300,000 for buildings at the Radcliffe Infirmary, for the professorial units and later created the "Nuffield Foundation" for more general educational purposes with ten millions. Lord Nuffield's biographers, P. W. Andrews and Elizabeth Brunner, estimated his gifts all in all up to 1955 at about 27 million pounds.

What is one to say of such munificence! I suppose that today's value of the money given in the creation of the Oxford chairs would be somewhere between 6 and 7 million pounds. It is well that these extraordinary events, for extraordinary they were, should be freshly remembered because for the first time really adequate finance had been provided for something that would never again be quite a dream. It would give a false impression to the youngest in our profession to-day if they got the notion that this new Oxford scheme fell on a wholly gaping and dumbfounded world. What was most astonishing was the generosity of its donor. The proposals themselves had been the current ideals of several of the longer sighted men in teaching hospital circles, especially in the provinces. We had come to despair of its actual creation. And here at last it was. It can well be imagined that Hugh Cairns was very quickly in the thick of the further planning for the best use to be made of these wonderful new opportunities. Hugh was a born planner; the news that something important needed organizing was to him what the smell of powder was said to be to the war horse. We can be sure that he gave it the enthusiastic and energetic propulsion at which he excelled. Buzzard was a wise man in his own deceptively quiet way; to most people he was better known for his timely silences, as Lord Moran said of him. I feel sure that his services not only as a go-between but as a catalyst should not be underestimated, but that he himself could have put through a scheme like this would be completely out of character. Hugh Cairns' knowledge and experience of the American teaching hospital and professorial procedure was needed to draft it in detail, his vigour to put it through.

It is extremely difficult to apportion credit fairly when looking back over these happenings. Although I think that the account which I have given is correct, that Hugh Cairns was the real begetter of the final scheme, it would be very odd indeed if it were quite so virtuoso a solo performance as it probably appears or will appear to those who did not know who was who in those days. Hugh was always one to enlist advice and to get the right people, people with different knowledge and different influences, people who could help, on his side. We can be quite sure that this was the case—they would be few, these advisers and helpers—but they would know their Oxford. He himself would be the last to minimize the help he had had from others, for example, at the London from the Canadian, (Sir) Arthur Ellis, a man whom he held in great

respect, and no less from Sir Douglas Veale in Oxford.

It was a foregone conclusion that Hugh himself would be the first Professor of Surgery. He had everything in his favour, familiarity with Oxford since the days of his Rhodes scholarship, his links with Balliol. His interest in research was well known, his writings showed his desire for perfection, he was a good surgeon, his reputation and charm of manner could be counted on to make his entrance, intrusion even, into a quiet hospital welcome. As if all this were not enough, he had the additional advantage of being an Australian and therefore a man who would be particularly attractive to post-graduates from the Dominions, not so restrained by tradition. His appointment as the first Nuffield Professor of Surgery was announced in January, 1937. Professor Macintosh's appointment to the Chair of Anaesthetics (the first in the Commonwealth) was made known in February, of Professor Chasser Moir in April, of Professor Witts in November. G. R. Girdlestone was to be Professor of Orthopaedics. It was not until 1938 when accommodation had been built, that Hugh left the London Hospital to which he had given so much of his best. In no time his charming house in Charlbury Road was as familiar to overseas visitors as had been his St. Johns Wood home. Here again one might see Hugh in slippered ease making notes or listening to music while Barbara ironed the family washing, both of them in the drawing room, and such children as happened to be at home listened or talked or read.

The War Years

After too short a time in which to establish the new Nuffield units, a matter of months since he did not leave London until the spring of 1938, came the first definite threats of war and Cairns had to turn his mind to a different sort of planning, in 1939 for the E.M.S., an office that he held first, then briefly he and I jointly before he relinquished the civilian side in 1940 to me to throw himself heart and soul into the Army Medical Service. He had been for a few years already consultant to the Army Hospital at Millbank and had made a deep impression on the authorities. Cairns told the story of the extremely efficient neurosurgical service that he so wisely built up for the Army in his paper "Neurosurgery in the British Army 1939-45", written for the special supplement of the *British Journal of Surgery* (1947) which he himself edited. It is so complete an account of what happened that little need be added. I would like though to remind you of the great thing that Cairns did in creating the mobile neurosurgical units—not in providing the personnel which he skimmed off the then few civilian neurosurgical centres leaving them to limp along as best they could—that was inevitable in such a war—but in giving them, or making available to them, diathermy and power suction and lighted brain retractors for use from Benghazi to the Rhine. Such luxury army surgeons had never had before. Do not forget that it speaks volumes for the respect and regard in which he was held by the War Office and the help that he had from a clever Director General, Sir William MacArthur, that he was able to get these things. No little because of them the units were able to obtain hitherto unheard of results in penetrating head wounds.

In February, 1940, the converted St. Hugh's College was opened as a Military Head Injuries Hospital and that again is too familiar a story to need retelling except that the youthful cream of British neurology, medical and surgical, worked there for longer or shorter times with Hugh. The acute brains of Sir Charles Symonds, D. Denny-Brown, and Ritchie Russell leading the medical, and Cecil Calvert the surgical division guided them faithfully and so well.

Frontal Sinus Injuries and Crash Helmets

In 1937 Cairns had already shown his interest in paranasal sinus injuries with dural tears. The meningitis, early or later, the cerebrospinal rhinorrhoea or the aerocoeles consequent to these injuries were beautifully described by him. In fact this 1937 paper is the best that he wrote on this subject though later he was to have so much more experience. It has the marks of leisurely writing that the havoc of war made impossible to achieve again. It has about it an aura of excitement, of creation as he built up his story with one case history after another. The accounts of his 13 cases left at the end a logical and satisfying picture of the way to recognize and to treat these conditions. We have to move on to the war years for the sequel to this paper and this took a different line. It was a vigorous attempt at the prevention of these injuries. Cairns, seeing so many of the Army's dispatch riders killed or maimed, carried out a vigorous campaign publicizing the advantages of the crash helmet in papers published in 1941, 1942, 1943, and 1946. In the 1943 paper he had Holbourn's assistance on the physics of brain injury and on the action of the helmets and the properties of the materials used in their construction. In the first year of the war three motor cyclists were killed each day, two of them Army riders. The first excitements of war and the blackout coupled sometimes with the recklessness of youth had led to this dreadful wastage. In the first 21 months 2,279 riders and pillion riders had been killed on the road. Here Hugh Cairns had a subject after his own heart,

vigorous campaign could be waged, practical vice given, planning done, people helped. He did very well indeed. The Army soon made the wearing of crash helmets compulsory (November, 1941). It was evident that the helmet, even if it was made of the better fibre type, was not a complete insurance against brain damage. But it reduced the number of skull fractures and by the helmet sliding along the ground with less friction than did the hairy scalp the force was spread over a longer period and the injury was less intense. That the crash helmet story is not yet ended is made plain by the discussion in the paper by Walpole Lewin and W. F. C. Kennedy (1956) published 15 years after Cairns' first communication. However, Cairns did a great work of benefaction to the motor cycle riders of these Islands and they should long bless him for the benefits of his advice.

I cannot tell in anything but the barest outline all the things that Hugh Cairns did during the war. Next to the crash helmet should come the penicillin story in which he applied the benefits of Howard Florey's industry and imaginative drive. Florey was as stubborn and indomitable as was Hugh himself. Obviously penicillin looked like being what the surgeons of the first world war had prayed for in vain. Florey knew that it would be needed in quantity—very well, it would be so provided and it was. Off Florey went with Cairns to North Africa and trials made in the Sicilian campaign proved so incredibly successful that a new phase in medicine had evidently arrived. It was characteristic of Hugh Cairns' careful mind that he was at once at work discovering the least amount of this new substance that would cure meningitis, how much would do harm. It was lucky no doubt that the amounts of penicillin available in the early months for clinical trial were small. This same care went into his work on meningococcal meningitis and again later into his partnership with Honor Smith on tuberculous meningitis. What was the minimum effective dose? How long did bacteriostatics or antiobiotics stay in the cerebrospinal fluid? Would it go there if it were given intravenously, intramuscularly? And in what proportions? and so on.

All this time Hugh had been very busy at the head injury hospital, St. Hugh's College, and had some of the burden of the Radcliffe to carry also, though Joe Pennybacker was a tremendous help there. He was Hugh's prop and staff in Oxford where he had loyally transferred himself with his chief. The unit would have collapsed had he not been there.

Aftermath to the "Dream"

To jump several years ahead we may ask the question, "What came of the original dream?" A basic desideratum was that the professors should not be much distracted by the teaching of undergraduates. At the Radcliffe Infirmary there had never been more than a handful of undergraduates and it was assumed that they would still be few, their numbers limited to the best on the original Hopkins plan of "Popsy" Welch's and Osler's day. But then came the war and a veritable deluge of students whose teaching had to be thickened by some valuable volunteer helpers such as Sir George Gask and Sir Arthur Hurst. Further, the war itself put a tremendous strain on a hospital with a depleted staff. The Radcliffe was in no worse case than others but the six war years were no time for the quiet pursuit of peace-time ideals. When the war was over many more medical students chose Oxford for clinical work, a turn that was not fully in keeping with Lord Nuffield's original desires, if I have understood them correctly. The magnificence (I use the word again) of his gifts was thrown somewhat into the shade by the awakening of the Government to the country's real educational needs. Through the University Grants Committee it began to pour money into our universities with the creation of whole-time professorships all over the place. And not only did it create chairs, it provided research budgets, not very fat ones, but much more than anyone had had before. We must conclude that the Nuffield plan was too good to be a lonely example. Oxford had made the model and it must be significant that Sir William Goodenough, whose Committee's report on the teaching hospitals roughed out the new plan for teaching hospitals, was a Nuffield man.

The new structure of the teaching of medicine is, however, different in a most important respect from the original "dream". It was concerned more with undergraduate than postgraduate training. In the Cairns' memoranda the training of picked men from our own and overseas schools who were to add by their brains and skills to that of the parent was a dominant feature. They were to have had opportunities in quietude both to learn and to add to knowledge without the small fry of an undergraduate school impeding the work of the laboratories. Perhaps it was a Baconian sort of dream after all, an unattainable one. I think that it would nevertheless have been carried through had it not been for the war. The bonds with workers in the ancillary and pre-medical subjects were never drawn quite tight enough nor did they get any considerable benefit from the new plan. But let us not forget how brightly the candle that Lord Nuffield had lighted burned in 1936 and later, with what enthusiasm the Nuffield professors had taken up their duties and carried them on until the war overwhelmed them. And when it was over we found ourselves living in a different

world with different needs and ideals not wholly reconcilable with those of 10 years earlier.

The Post-war Years

I have already mentioned the whole-hearted way in which Hugh Cairns had seized the new opportunities for the treatment of hitherto fatal intracranial infections. He continued this with the same enthusiasm in "Nuffield I", now with civilian cases. The big new development was the discovery that *M. tuberculosis* was susceptible to streptomycin. New hope could be offered to those with that hitherto disheartening disease, tuberculous meningitis. Nothing does Cairns and his associates more credit than the attack on it which they carried out. Perhaps this is the time to mention Cairns' flair for team work, for getting good people to work with him. It was characteristic. He was fortunate in this instance in having the help of the brilliant and indefatigable Honor Smith, and of Peter Daniel and R. L. Vollum. One has only to read again their papers from 1949 onwards to appreciate the immense care that had been taken to cover all points in the management of these cases. I might add a special word of praise for the endurance of all, not only Cairns' own staff but of those in the wards and in the laboratories in the day-by-day and months-long struggle towards success in case after case. I do not think that I overpraise Cairns when I say that he was the first to demonstrate the critically important part which neurosurgery could play in the treatment of meningitis and of the tuberculous type in particular, in the demonstration of spinal block and in devising ways of correcting it. It was at least path-finding work. Honor Smith's later work devised means of preventing its occurrence.

Cairns was becoming more and more interested in a quite different and more difficult subject, the psychological disorders caused by tumours and in an operative approach to mental disorder. His interest is apparent in his 1936 follow-up of Cushing's cases but five years later he and his associates leaped to the front by his description of "akinetic mutism" (1941) as evidenced by a child with a cyst of the third ventricle. In this observation he had the help of R. C. Oldfield, of the Psychological Research Laboratory at Cambridge (now Professor of Psychology at Oxford), of Joe Pennybacker, and Donald Whitteridge (now Professor of Physiology at Edinburgh). It was an exceptionally powerful team. Their observation, so well and strikingly named, has not ceased to excite great interest. It made a great impression on continental neurology, judged by the references made in the discussion on consciousness at the Brussels International Neurological Congress (1957). Cairns carried his interest in mental and personality changes caused by low level lesions to his Victor Horsley Lecture (1952) on these disturbances in diencephalic and brain-stem lesions, using a carefully selected group of cases, telling an interesting story. In the same year there appeared his description of bilateral anterior cingulectomy for mental disorders in 29 patients. In the psychotics, improvement was temporary but several good results were obtained in obsessional cases and anxiety states with bad effects on personality much less than those which followed classical leucotomies. His interest in psychology emerged again in his valuable paper with W. H. Mosberg on colloid cysts of the third ventricle and even more so when he turned his attention to hemispherectomy for hemiplegic epilepsy in children and young people—this the child of his Johannesberg pupil, Krynauw's, bright brain.

Conclusion

It has been impossible to do much more than sample Hugh Cairns' contributions to neurology and to surgery. It will have been observed that more attention has been paid to the work of his first 20 years than to his later and latest. This has been a deliberate choice because choice there had to be. His beginnings are less familiar to all but a few members of the society under whose auspices this lecture has been so very properly founded.

His death, on July 18, 1952, soon after his 56th birthday cut him off when he was sailing on the full flood. All that he had done in the past was carrying him forward, it seemed, in a widening field. Hugh would never have lost control of his destiny. He was too shrewd for that, too practical. He left behind him an impressive achievement. Had he died 10 years earlier, at the war's end, we should still have had cause for admiration. But he was full of plans for the future when he died. How sorely we have missed his delightful presence these last years, how much he could still contribute not only to neurological surgery but in our national counsels on education, on university affairs, and in something else, the strengthening by his friendship of the ties of Dominion and international scientific relations. It must have been a joy to him to revisit the scenes of his youth when he returned to Australasia as the first Sims Professor in 1947-48 and later to Africa to spread the gospel of the correct treatment of tuberculous meningitis.

The man himself most of my audience knew; several have worked with him. They know what I mean when I speak of Hugh's sincerity, his charm, his industry, his physical strength, his mental vigour, his candour, above all perhaps a certain boyish naïveté and a sense of humour that would break

though even when he was looking his grimmest, driving his hardest. One forgave him even when he was driving a hard bargain—and he knew very well how to do that.

Of his charm it should be said that this was as natural to him as his delightful voice, and, though I think that he was conscious of them, he did not use those gifts, as is the danger, insincerely. He had too independent, too individual, too critical a mind to fall in with anything second rate. Though I cannot say that we invariably agreed, our differences were slight, I scarcely now remember what they were, we were one on everything that mattered. I should know because we conferred so fully on major developments. Those who met him in head-on collision might well have different ideas of him, for he had a sort of puritanical belief in the rightness of his own causes. At times was he not a little insensitive to the views and claims of others? Maybe. He was kindness itself in all his traffic with me. I can only add to what I wrote in 1952 that I loved the man.

The writer is deeply indebted to many people, principally to Lady Cairns, Lord Nuffield, Sir Douglas Veale, Sir Arthur Ellis, and in Adelaide to Leonard Lindon, Trevor Dinning, Hugh Cairns' aunt and uncle, Mr. and Mrs. Bell, and Mr. West. I must thank also Professor Witts, Professor Sir R. Macintosh, Mr. Douglas Northfield, and Mr. Joe Pennybacker for helpful information.

BIBLIOGRAPHY

HUGH CAIRNS

Collected Papers

1925-1938

The collected papers are available in bound volumes at the Radcliffe Infirmary, Oxford, but the journal references below will enable readers to trace individual papers.

Observations on the Etiology and Treatment of Cystitis (1925). *Brit. J. Surg.*, **13**, 78.

Renal Colic as a Late Complication of Nephrectomy (1925). *Ibid.*, **13**, 178.

Heredity in Polycystic Disease of the Kidneys (1925). *Quart J. Med.*, **18**, 359.

Neoplasms of the Testicle [Hunterian Lecture] (1926). *Lancet*, **1**, 845.

The Treatment of Intracranial Tumours (1928). *London Hosp. Gaz.*, **31**, 132.

The Treatment of Head Injuries (1928). *Lancet*, **1**, 566 and 617.

The Treatment of the Sequels of Head Injuries [with W. Russell Brain] (1928). *Ibid.*, **1**, 668.

A Study of Intracranial Surgery (1929). *Spec. Rep. Ser. med. Res. Coun.* (*Lond.*), No. 125.

Observations on the Localization of Intracranial Tumours (1929). *Lancet*, **1**, 600. *Arch. Surg.* (*Chicago*), **18**, 1936.

The Ocular Manifestations of Head Injuries (1929). *Trans. ophthal. Soc.* (*U.K.*), **49**, 314.

Discussion on Diseases of the Pituitary Body (1929). *Proc. roy. Soc. Med.*, **23**, 213.

Experimental Observations on the Action of Radon on the Spinal Cord [with J. F. Fulton] (1930). *Lancet*, **2**, 16.

Spinal Metastases in a Case of Cerebral Glioma of the Type Known as Astrocytoma Fibrillare [with D. S. Russell] (1930). *J. Path. Bact.*, **33**, 383.

The Surgery of the Spinal Cord. Discussion. Section of Surgery, R.S.M. (1930). *Proc. roy. Soc. Med.*, **23**, 403.

Brain Abscess from the Point of View of the Neurological Surgeon (1930). *Ibid.*, **23**, 1049.

Le Traitement des Tumeurs Intracraniennes par le Radium, en particulier en ce qui concerne le Glioblastome Multiforme [with Stanford Cade] (1931). *Rev. neurol.*, **2**, 382.

Observations on the Treatment of Ependymal Gliomas of the Spinal Cord [with George Riddoch] (1931). *Brain*, **54**, 117.

Intracranial and Spinal Metastases in Gliomas of the Brain [with Dorothy S. Russell] (1931). *Ibid.*, **54**, 377.

Treatment of Injuries of the Spinal Cord (1931). *Index of Treatment*, p. 856. John Wright, Bristol.

Observations on the Treatment of Orbital Osteoma, with Report of a Case [with Norman Patterson] (1931). *Brit. J. Ophthal.*, **15**, 458.

Acoustic Neurinoma of Right Cerebello-pontine Angle. Complete Removal. Spontaneous Recovery from Post-operative Facial Palsy (1931). *Proc. roy. Soc. Med.*, **25**, 35.

Diagnosis and Treatment of Pineal Tumours [with Wilfred Harris] (1932). *Lancet*, **1**, 3.

Nurses and Brain Surgery (1932). *Nursing Times*, **28**, 1026, 1053, 1077.

Cystic Haemangioma of the Cerebellum. Operation with Removal of Mural Nodule [with Douglas McAlpine] (1931-32). *Proc. roy. Soc. Med.*, **25**, 30.

Observations on the Results of Division of the Eighth Nerve in the Treatment of Aural Vertigo [with W. Russell Brain] (1933). *Ibid.*, **26**, 689. (1933) *Lancet*, **1**, 946.

Subdural False Membrane or Haematoma (Pachymeningitis Interna Haemorrhagica) in Carcinomatosis and Sarcomatosis of the Dura Mater [with Dorothy S. Russell] (1934). *Brain.*, **57**, 32.

Discussion on the Diagnosis and Treatment of Abscess of the Brain [with Charles Donald] (1934). *Proc. roy. Soc. Med.*, **27**, 1643.

Recent Advances in Neurosurgery (1935). *J. roy. nav. med. Serv.*, **21**, 78.

Prognosis of Pituitary Tumours (1935). *Lancet*, **2**, 1310, 1363.

The Management of Intracranial Tumour [with D. Denny-Brown] (1935). *Brit. med. J.*, **2**, 1162.

Störung der Sekretion und Resorption der Cerebrospinalflüssigkeit und ihre Behandlung (1935). *Dtsch. Z. Nervenheilk.*, **138**, 180.

Accessory Methods of Diagnosis in Intracranial Tumour and Allied Diseases (1935). *Trans. med. Soc. Lond.*, **58**, 50.

The Ultimate Results of Operations for Intracranial Tumours (1936). *Yale J. Biol. Med.*, **8**, 421.

Spätergebnisse der operativen Behandlung von Hirngeschwülsten [German translation of shortened version of above] (1936). *Nervenarzt*, **9**, 401.

Late Results in the Operative Treatment of Intracranial Tumours [English version of above] (1936). *Lancet*, **1**, 1223.

The Radiological Appearances of Meningiomas. Discussion on the Value of Radiology in Neurosurgery. Section of Radiology, R.S.M. (1936). *Proc. roy. Soc. Med.*, **29**, 1166.

Brain Tumour [with C. P. Symonds] (1936). *The British Encyclopaedia of Medical Practice*, Vol. 2, p. 619. Butterworth, London.

Brain Abscess [with C. P. Symonds] (1936). *Ibid.*, Vol. 2, p. 597.

Ergebnisse der Behandlung intrakranieller Tumoren (1937). *Schweiz. med. Wschr.*, **67**, 1037.

The Wet Film Technique in the Histological Diagnosis of Intracranial Tumours: A Rapid Method [with D. S. Russell and H. Krayenbühl] (1937). *J. Path. Bact.*, **45**, 501.

Injuries of the Frontal and Ethmoidal Sinuses, with Special Reference to Cerebrospinal Rhinorrhoea and Aerocele (1937). *J. Laryng.*, **52**, 589.

Observations on the Pathology of Ménière's Syndrome [with C. S. Hallpike] (1938). *Ibid.*, **53**, 625. (1938) *Proc. roy. Soc. Med.*, **31**, 1317.

Peripheral Ocular Palsies from the Neurosurgical Point of View (1938). *Trans. ophthal. Soc.* (*U.K.*), **58**, 464.

1939-1945

Bacterial Infection during Intracranial Operations (1939). *Lancet*, **1**, 1193.

Obituary—Harvey Cushing (1939). *Ibid.*, **2**, 856.

Raised Intracranial Pressure: Hydrocephalic and Vascular Factors (1939). *Brit. J. Surg.*, **27**, 275.

Central Nervous System [with M. H. Jupe] (1939). In *A Textbook of X-ray Diagnosis*, by British Authors, ed. S. C. Shanks, P. Kerley, and E. W. Twining. Vol. III, p. 1. Lewis, London.

Treatment of Head Injuries in War (1940). *Brit. med. J.*, **1**, 1029.

Treatment of Gunshot Wounds of Peripheral Nerves [with J. Z. Young] (1940). *Lancet*, **2**, 123.

Brain Fungus [with P. Ascroft and R. Hannah]. Discussion on Gunshot Wounds of the Head, 27th Meeting of the Society of British Neurological Surgeons (1940). *J. Neurol. Psychiat.*, **3**, 350.
Gunshot Wounds of the Head in 1940 (1941). *J. roy. Army med. Cps*, **76**, 12.
Head Injuries in Motor-cyclists: The Importance of the Crash Helmet (1941). *Brit. med. J.*, **2**, 465.
Obituary—O. Foerster (1941). *Ibid.*, **2**, 634.
El Tratamiento de los Abscesos Cerebrales (1941). *Act. esp. Neurol.*, **2**, 239.
Head Injuries (1941). *J. roy. Army med. Cps*, **77**, 212.
Akinetic Mutism with an Epidermoid Cyst of the Third Ventricle [with R. C. Oldfield, J. B. Pennybacker, and D. Whitteridge] (1941). *Brain*, **64**, 273.
Pathology of Closed Head Injuries in the Acute State. Discussion on Closed Head Injuries, 28th Meeting of the Society of British Neurological Surgeons (1941). *J. Neurol. Psychiat.*, **4**, 269.
Discussion on Rehabilitation after Injuries to the Central Nervous System (1942). *Proc. roy. Soc. Med.*, **35**, 299.
Rehabilitation after Head Injuries (1942). *Brit. J. phys. Med.*, **5**, 84.
The Vascular Aspects of Head Injuries (1942). *Lisboa méd.*, **19**, 375.
Head Injuries in War, with Especial Reference to Gunshot Wounds (1942). *War Med.* (*Chicago*), **2**, 772.
Discussion on Injuries of the Frontal and Ethomoidal Sinuses (1942). *Proc. roy. Soc. Med.*, **35**, 809.
Planning for the Treatment of Head Injuries (1943). *Brit. med. J.*, **1**, 313.
A Review of Recent German Work on Gunshot Wounds of the Head [with E. Guttmann] (1943). *Bull. War Med.*, **3**, 477.
Head Injuries in Motor-cyclists, with Special Reference to Crash Helmets [with H. Holbourn] (1943). *Brit. med. J.*, **1**, 591.
A Preliminary Report to the War Office and the Medical Research Council on Investigations Concerning the Use of Penicillin in War Wounds [with H. W. Florey]. (Section on Head Wounds with K. C. Eden and J. Shoreston.) War Office A.M.D.7/90d/43, pp. 3 and 97.
Penicillin in Head and Spinal Wounds (1944). *Brit. J. Surg.*, **32**, 199. Penicillin Issue.
Gunshot Wounds of the Head in the Acute Stage (1944). *Brit. med. J.*, **1**, 33.
Pneumococcal Meningitis Treated with Penicillin [with E. S. Duthie, W. S. Lewin, and H. V. Smith] (1944). *Lancet*, **1**, 655.
The Organization for Treatment of Head Wounds in the British Army (1945). *Brit. med. Bull.*, **3**, 9.
Chemotherapy in Brain Wounds and Meningitis (1945). *Army med. Dept. Bull.* (*Lond.*), Suppl. No. 20.

1946-1952

Chemotherapy of Pneumococcal Meningitis [with H. V. Smith and E. S. Duthie] (1946). *Lancet*, **1**, 185.
Investigations on Head Injuries in Britain during the Second World War (1946). *Schweiz. med. Wschr.*, **76**, 865.
The Scope of Neurosurgery (1946). *Practitioner*, **156**, 2.
Obituary—Sir Farquhar Buzzard (1946). *Nature* (*Lond.*), **157**, 218.
Obituary—Walter Edward Dandy (1946). *Lancet*, **1**, 718.
Crash Helmets (1946). *Brit. med. J.*, **2**, 322.
Diagnosis of Tumours of the Central Nervous System (1946). *Bristol med.-chir. J.*, **63**, 73.
Intrathecal Streptomycin in Meningitis: Clinical Trial in Tuberculous, Coliform and Other Infections [with E. S. Duthie and H. V. Smith] (1946). *Lancet*, **2**, 153.
Cerebral Arteritis and Phlebitis in Pneumococcal Meningitis [with D. S. Russell] (1946). *J. Path. Bact.*, **58**, 649.
Discussion on the Chemotherapy of Meningitis Secondary to Infection of the Ear and Nasal Sinuses [with H. V. Smith and F. Schiller] (1946). *Proc. roy. Soc. Med.*, **39**, 613.
Neurosurgery in the British Army, 1939-1945 (1947). *Brit. J. Surg., War Surgery Suppl. No.* 1; *Wounds of the Head*, p. 9.
Localized Hydrocephalus following Penetrating Wounds of the Ventricle [with P. M. Daniel, R. T. Johnson, and G. B. Northcroft] (1947). *Ibid.*, p. 187.
Complications of Head Wounds, with Especial Reference to Infection [with C. A. Calvert, P. M. Daniel, and G. B. Northcroft] (1947). *Ibid.*, p. 198.
Penicillin in Suppurative Lesions of the Brain and Meninges (1947). *Brain*, **70**, 251.
Penicillin in Suppurative Conditions of the Brain and Meninges. Discussion on Penicillin in Neurology (1947). *Proc. roy. Soc. Med.*, **40**, 681.
Penicillin in the Prevention of Infection during Operations on the Brain and Spinal Cord [with J. B. Pennybacker and L. M. Taylor] (1947). *Lancet*, **2**, 159.
Polar Spongioblastomas [with D. S. Russell] (1947). *Arch. Histol.* (*B. Aires*), **3**, 423.
George Adlington Syme Oration: The Progress of Surgery, with Especial Reference to Intracranial Surgery (1948). *Aust. N.Z.J. Surg.*, **18**, 3.
Treatment of Tuberculous Meningitis with Streptomycin [with H. V. Smith and R. L. Vollum] (1948). *Lancet*, **1**, 627.
Late Results of Gunshot Wounds of the Head (1948). *N.Z. med. J.*, **47**, 95.
The Treatment of Purulent Pachymeningitis and Subdural Suppuration, with Special Reference to Penicillin [with F. Schiller and D. S. Russell] (1948). *J. Neurol. Neurosurg. Psychiat.*, **11**, 143.
Obituary—G. T. Western (1948). *Lancet*, **2**, 711.
Purulent Pachymeningitis [with F. Schiller] (1948). *Proc. roy. Soc. Med.*, **41**, 805.
Penicillin: Principles of Application in Surgical Infections (1948). Proc. 12th Congr. Soc. Int. Chirurg., London, 1947, p. 229. Brussels.
Brain—Tumours and Technique [with J. B. Pennybacker] (1948). *British Surgical Practice*, Vol. 2, p. 420. Butterworth, London.
Clinical Records in Surgery (1948). *Hospital* (*Lond.*), **44**, 101. (1949) *J. roy. Army med. Cps*, **93**, 218.
A Review of the Treatment of Tuberculous Meningitis with Streptomycin [with Margaret Taylor]. Discussion on Streptomycin in Meningitis (1949). *Proc. roy. Soc. Med.*, **42**, 155.
Surgical Aspects of Meningitis (1949). *Brit. med. J.*, **1**, 969.
The Student's Objective (1949). *Lancet*, **2**, 665.
On Becoming a Good Doctor (1949). *Brit. med. J.*, **2**, 805.
The Effects of Lesions in the Cingular Gyrus and Adjacent Areas in Monkeys [with P. Glees, J. Cole, and C. W. M. Whitty] (1950). *J. Neurol. Neurosurg. Psychiat.*, **13**, 178.
Tuberculous Meningitis [with H. V. Smith and R. L. Vollum] (1950). *J. Amer. med. Ass.*, **144**, 92.
Mental Disorders with Tumours of the Pons (1950). *Folia psychiat. neerl.*, **53**, 193.
Brain Abscess [with C. P. Symonds] (1950). In *The British Encyclopaedia of Medical Practice*, 2nd ed., Vol. 3, p. 67. Butterworth, London.
Results in 130 Cases of Acoustic Neurinoma [with J. B. Pennybacker]. Symposium on the Results of Operations on Acoustic Neuromas, 38th Meeting of the Society of British Neurological Surgeons (1950). *J. Neurol. Neurosurg. Psychiat.*, **13**, 272.
Editorial—Neurosurgery (1950). *Med. ill.* (*Lond.*), **4**, xi.
Fractures of the Sphenoidal Sinus with Cerebrospinal Rhinorrhoea [with W. Lewin] (1951). *Brit. med. J.*, **1**, 1.
A Symposium on the Operative Treatment of Mental Disorders. I: The Historical and Surgical Aspects (1951). *Oxford med. Sch. Gaz.*, **3**, 3.
Colloid Cyst of the Third Ventricle [with W. H. Mosberg] (1951). *Surg. Gynec. Obstet.*, **92**, 545.
Hemispherectomy in the Treatment of Infantile Hemiplegia [with M. A. Davidson] (1951). *Lancet*, **2**, 411.
Neurosurgical Methods in the Treatment of Tuberculous Meningitis, with a note on some Unusual Manifestations of the Disease (1951). *Arch. Dis. Childh.*, **26**, 373.
Neuere Fortschritte in der Behandlung von Kopfverletzungen (1952). *Dtsch. med. J.*, **3**, 58.
Anterior Cingulectomy in the Treatment of Mental Disease [with C.W.M. Whitty, J. E. Duffield, and P. M. Tow] (1952). *Lancet*, **1**, 475.
Tuberculosis of the Central Nervous System [with H. V. Smith] (1952). In *Modern Practice in Tuberculosis*, ed. T. H. Sellors and J. L. Livingstone, Vol. 2, p. 353. Butterworth, London.
Neurosurgery (1952). In *Careers in Medicine*, p. 105, ed. P. O. Williams. Hodder & Stoughton, London.
Disturbances of Consciousness with Lesions of the Brain-Stem and Diencephalon (1952). *Brain*, **75**, 109.
Temporary Depression of Cortical Function by Local Anaesthetic and Cooling [with J. Cole, H. G. Epstein, M. Gardner, and P. Glees] (1953). *J. Physiol.* (*Lond.*), **119**, 44P. [Posthumous.]

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CHANGES IN HUMAN MUSCLES AFTER PERMANENT TENOTOMY*

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There is an extensive literature on the "disuse" atrophy of muscle produced by a variety of techniques, in a variety of experimental animals and with different muscles, but usually those of the calf, forming the subject of study. Accounts of this condition in human muscles, however, appear to be limited to passing references in the clinical literature to the wasting which follows the immobilization of limbs and to a brief note by Smith (1928) on the histological structure of a muscle attached solely to the shaft of the fibula. The great difficulty of obtaining suitable human material for weight loss and histological studies is obvious, though the possibilities of investigating disuse phenomena in the muscles after tenotomy of amputation stumps does not appear to have been appreciated. Admittedly the normal and affected limbs of deceased amputees are rarely available for unhurried dissection but when this does become possible the opportunity should be taken of adding to our data on atrophy after tenotomy in human muscles. Recently the authors had an opportunity of performing two such dissections and the observations made on this material form the subject matter of this paper.

MATERIAL AND METHODS

Subject 1.—The right hand of H.T., a male, aged 76, had been amputated through the radio-carpal joint 20 years before death. Movements at and above the elbow joint were not impaired. The body was embalmed within 24 hours of death and then stored in formalin. When dissected, the normal and affected arms were in an excellent state of preservation. Dissection revealed normal radio-ulnar joints though pronation and supination were limited in range. On the involved side the severed tendons had become adherent to the distal extremities of the radius and ulna. The arrangement of the forearm muscles permitted their subdivision into four groups.

Group 1.—Tenotomized muscles taking origin below the elbow joint of which the severed tendons were adherent to the stump; these were unable to shorten. This group was represented by the abductor pollicis longus, extensor pollicis brevis, extensor pollicis longus, flexor pollicis longus, flexor digitorum profundus, and extensor indicis proprius.

Group 2.—Tenotomized muscles arising from the lower end of the humerus of which the tendons originally passed to an attachment in the hand but were now adherent to the stump; normally this group contributes little to movements at the elbow joint. However, the disposition of the muscles with reference to this joint was such that, during life, they would have been affected by movements of the forearm and would also have been free to shorten. This group could be further subdivided into:

(a) Those muscles taking origin solely from the humerus (radial flexors and extensors of the wrist, palmaris longus, extensor digitorum communis); and (b) those muscles gaining an additional origin from one of the bones of the forearm (ulnar flexor and extensor of the wrist and flexor digitorum sublimis).

Group 3.—The supinator and pronators of which the attachments were undisturbed but specific functions were curtailed. This group could be further subdivided into the humeral heads of the pronator teres and supinator, which cross the elbow joint, and the deep heads of these muscles plus the pronator quadratus which join the radius and the ulna.

Group 4.—Muscles with attachments and functions which were not disturbed by the amputation, *e.g.*, the brachioradialis.

Each muscle was carefully isolated and removed, tendons being divided at corresponding levels on the two sides. The muscles were immediately weighed and then transferred to 10% formalin. There are several sources of error in obtaining the weight of wet specimens and in employing, as was the method adopted in this study, the weight of the corresponding normal muscle as the pre-operative weight of the involved muscle for calculating the percentage atrophy. Those errors have been detailed by Langley (1916, 1917) and Langley and Hashimoto (1918). All the precautions outlined by them were observed in the present enquiry.

The muscles were submitted to a standard histological procedure. After fixation in formalin a block was taken at the mid-point of the belly of each muscle. After embedding the material in paraffin in the usual manner, transverse sections, 10μ in thickness, were prepared from

*This work was assisted by a grant from the National Health and Medical Research Council of Australia.

the faces of the block. The remainder of the block was then sectioned longitudinally at 10μ. The sections were stained with haematoxylin and eosin and Van Gieson.

Subject 2.—S.W., a male, aged 40 years, had a mid-thigh amputation on the right side 10 months before death. The dissection of this subject was performed in the necropsy room. The level of the amputation prevented a study of weight loss but provided material for the histological examination of tenotomized muscle. Blocks of tissue were removed from the affected and normal hamstring muscles. In this case, however, no muscles had been rendered completely functionless by the operation. The hamstrings, for example, continued to aid extension at the hip joint. The muscle tissue removed for histological study was prepared in the same way as that obtained from Subject 1.

MACROSCOPIC FEATURES

The tenotomized muscles (Groups 1 and 2) were distinctly paler than the normal muscles but despite this they retained their general form and a colour and texture which identified them as muscles. There was no suggestion of a yellowish or translucent appearance and no macroscopic evidence of any conversion into ill-defined fibrous tissue.

The most conspicuous change in the affected muscles was a reduction in size and weight. The extent of this atrophy for the different muscles is given in Table I. In the group most severely affected by the amputation (Group 1), the weight loss varied from 53 to 62% while the atrophy in the Group 2 muscles varied from 50 to 69% (palmaris longus 39%). The marked atrophy in the latter group suggests that these muscles were not significantly affected by movement at the elbow joint.

The pronator teres and supinator which joined the radius and ulna but were also attached to the lower end of the humerus showed an atrophy of 16 and 18% respectively. On the other hand, the pronator quadratus, which was attached solely to the radius and ulna, had atrophied by 28%. It is

TABLE I

WEIGHT LOSS

Muscle	Weight (g.)		Percentage Atrophy
	Left Normal	Right Affected	
Group 1			
Extensor pollicis longus	7·1	2·7	62
Extensor pollicis brevis Abductor pollicis longus	15·4	7·3	53
Extensor indicis proprius	5·8	2·2	62
Flexor pollicis longus	13·9	6·1	56
Flexor digitorum profundus	85·4	34·7	59
Group 2(*a*)			
Extensor carpi radialis longus	38·4	15·6	59
Extensor carpi radialis brevis	28·7	14·2	51
Extensor digitorum communis	47·7	18·3	62
Flexor carpi radialis	21·3	11·8	45
Palmaris longus	4·6	2·8	39
Group 2(*b*)			
Extensor carpi ulnaris	22·0	10·7	51
Flexor carpi ulnaris	30·8	15·4	50
Flexor digitorum sublimis	69·6	21·5	69
Group 3			
Pronator teres	34·9	29·3	16
Pronator quadratus	13·4	9·6	28
Supinator	22·2	18·1	18
Group 4			
Brachioradialis	52·3	52	1

TABLE II

PERCENTAGE WEIGHT LOSS IN ANIMALS

Author	Animal	Muscle	Procedure	Days/Percentage Weight Loss
Knowlton and Hines	Rat	Gastrocnemius	Tenotomy	7/17; 14/29; 21/22; 42/22
Solandt *et al.*	Rat	Gastrocnemius	Immobilization by pinning joints	10-14/40-50. Remained at or near this reduced rate for the duration of the experiment—41 days
Fischer	Rat	Gastrocnemius soleus	Tenotomy	9/20; 10/32; 23/46·5; 28/54; 32/48
Carey *et al.*	Rat	Gastrocnemius	Tenotomy	21-30/30-50
Davenport and Ranson	Rat	Gastrocnemius	Tenotomy	16/20
	Cat	Gastrocnemius	Tenotomy	17/21
Eccles	Cat	Gastrocnemius soleus, tibialis anterior, extensor digitorum longus	Tenotomy Cord isolation	Duration of experiments 3 weeks. Tenotomy and cord isolation cause "a similar weight loss of about 50% in soleus, but in the other muscles the weight loss resulting from tenotomy is only about 20% as compared with the 40% loss with disuse atrophy"
Thompson	Rabbit	Calf Thigh	Cast immobilization (a) limb bearing weight (b) limb not bearing weight	Calf 42/30; thigh 42/<5-10 Calf 42/45; thigh 42/20-25
Fischer and Ramsey	Rabbit	Gastrocnemius	Tenotomy Cast immobilization	22-30/46 22-30/39
Lippmann and Selig	Rabbit	Semitendinosus Gastrocnemius	Tenotomy Immobilization	6/24-30; 7/32-33; 12/46-54; 14/47-48; 20/69; 35/54 32/3
Audova	Rabbit	Gastrocnemius soleus	Tenotomy	6/+0·5; 14/19·1; 28/39·9; 56/50; 84/55·4; 123/56·6: all mean values
Lipschütz and Audova (1921)	Rabbit	Gastrocnemius soleus	Tenotomy	12-16/0·1-41·8; 28/28·9-45·6; 56/46·3-52·5; 84/41·5-65·6; 123/52·7-62·1
Hirohasi	Dog	Gastrocnemius	Tenotomy, cast immobilization	1 month/19·3-57·7. Average 40% for 5 specimens 1 month/4·4-42·0. Average 26·6% for 5 specimens
		"Shank" muscles	Tenotomy	7/4·1; 11·2; 17·5. 14/2·8; 6·4; 15·3. 21/14·4; 15·3; 22·2. 1 month/18·0; 28·4; 32·8. 2 months/9·0; 9·6; 27·4
				7/+7; 7; 7·4. 14/+3·8; 7·8; 23·0. 21/+1·5; 1·6; 20·1.
			Cast immobilization	1 month/7·3; 19·3; 31·9. 2 months/+5·8; 11·4; 32·7
Chor and Dolkart	Monkey	Gastrocnemius soleus	Cast immobilization	7/4·9; 14/12·8; 21/15·7; 28/27·1; 42/29·8; 70/32·5

possible that free elbow movement may have been responsible for some of the difference in weight loss between the two groups though this difference is hardly significant.

In contradistinction to the foregoing muscles the weight of the brachioradialis, which functions as a flexor of the elbow joint and was unaffected by the operation, differed by 1% on the two sides which is well within the range of normality.

A comparison of the atrophy recorded for Groups 1 and 2 on the one hand and Group 3 on the other does, however, reveal a correlation between the degree of the atrophy and the relationship of the muscles to functioning joints. The atrophy was greatest in those muscles which were not, or were but little, affected by joint movements and least marked in those of which the physiology was constantly and significantly modified by such movements (Group 3). In other words, the degree of atrophy was related to the amount of disuse to which the muscle was subjected.

The findings for the tenotomized human muscles are in general agreement with those reported for experimental animals (see Table II) by Audova (1922), Lippmann and Selig (1928), Chor and Dolkart (1936), Hirohasi (1938), Fischer (1941), and Eccles (soleus, 1944), but the weight loss was somewhat greater in the human material than that recorded by Thompson (1934), Chor and Dolkart (1936), Hirohasi (1938), Solandt, Partridge, and Hunter (1943), Fischer and Ramsey (1946), but Carey, Haushalter, Massopust, Garofalo, Lynch, Tabat, and Socoloff (1947), Davenport and Ranson (1930), Knowlton and Hines (1940), and Eccles (tibialis anterior and extensor digitorum longus, 1944), on the other hand, reported a much less severe atrophy in their material. It is to be remembered, however, that the duration of the tenotomy in the human material was very much greater than that employed in any of the experimental investigations.

MICROSCOPIC FEATURES OF THE TENOTOMIZED MUSCLES

The general overall pattern of the muscle as seen in transverse section was retained.

Reaction of the Extrafusal Fibre to Tenotomy

Calibre.—The most characteristic change in the morphology of the fibre involved a loss of sarcoplasm and a reduction in its calibre (Figs. 1 to 4). Though this atrophy was generalized throughout the muscles examined, some fibres were affected more than others in the same muscle while individual variations in the degree of atrophy among fibres in the same bundle were not uncommon (Figs. 1, 2). Others to comment on these irregularities were Thompson (1934), Tower (1937), and Carey *et al.* (1947). In some regions the atrophy was extreme, all the fibres being threadlike and in obvious contrast to the surrounding fibres.

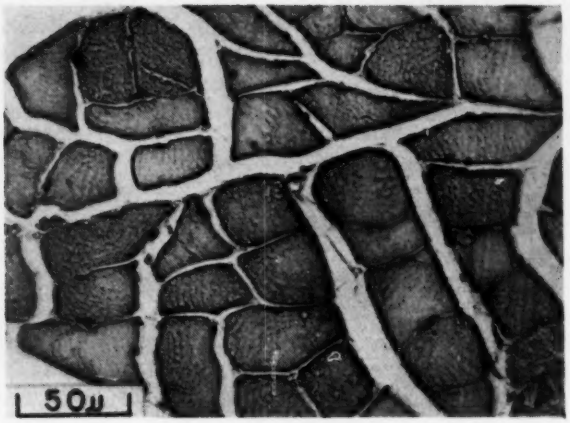
Fibre atrophy was observed by Krauss (1888), Chor and Dolkart (1936), and Tower (1937), but Davenport and Ranson (1930) stated that "the atrophy which was indicated by loss of weight was not apparent microscopically" nor could Smith (1928) find any evidence of fibre atrophy.

Subsarcolemmal Nuclei.—The nuclei appeared to be unaltered by tenotomy. Round, oval, and extremely elongated forms were seen, the nucleoli were not increased, and there was no evidence of mitotic activity. Centrally placed nuclei were present but these were no more numerous than in the controls. In this respect the flexor digitorum sublimis was exceptional in that it presented large numbers of central nuclei associated with a high proportion of thin muscle fibres. Deeply situated nuclei were reported by Davenport and Ranson (1930) in both normal and affected muscles.

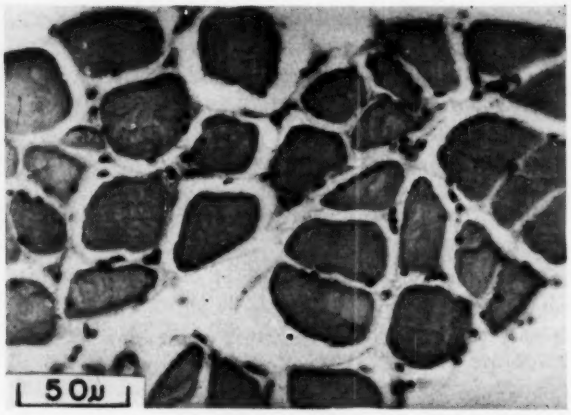
Tower (1937) described a progressive atrophy and disappearance of the subsarcolemmal nuclei, Froboese (1922) a nuclear increase, and Davenport and Ranson (1930) "A slight but not marked increase", with the nuclei in some fibres appearing a little swollen and staining a little less intensely than normal. On the other hand Krauss (1888) could not detect any nuclear proliferation, while Chor and Dolkart (1936) reported the fibre nuclei as being "not obviously increased in number nor altered in size" and without evidence of mitosis.

Striations.—The striations (Fig. 3) were not uniformly stained in either the normal or the affected muscles which made it difficult to determine whether their absence or fading in the latter was to be attributed to the tenotomy or to vagaries in the staining. It is an impression only that myofibrils lacking in distinct cross striations were more common in the affected muscles. Both transverse and longitudinal striations were, however, well preserved in most of the fibres of all the affected muscles and were often more intensely stained than in the normal fibres. In the poorly stained fibres the longitudinal fibrillation was more distinct than the cross striation. Hensen's discs were clearly visible in the well-stained fibres.

The cross striations were preserved in Chor and Dolkart's (1936) material but they were unable to observe longitudinal striations. On the contrary, the longitudinal striation was more pronounced and the cross striation blurred in Davenport and



(a)



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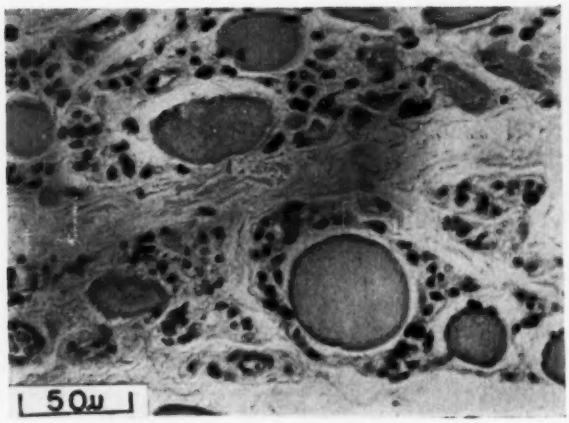
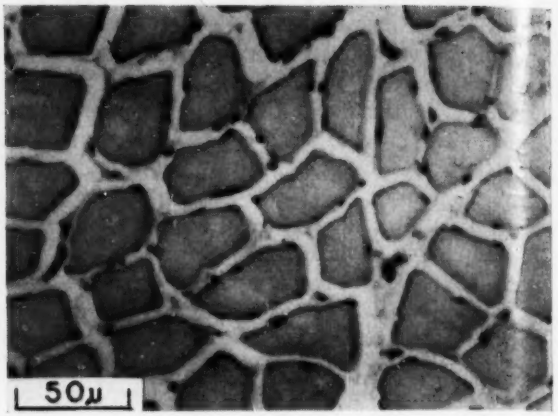
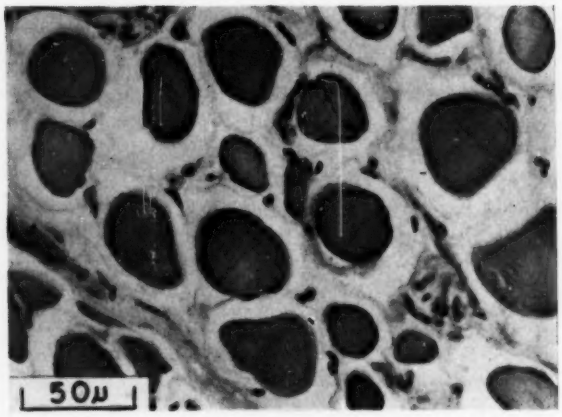


(c)

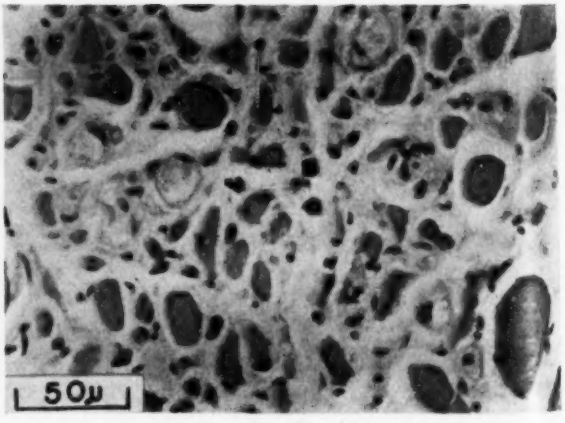
FIG. 1.—Transverse sections from the normal (a), and tenotomized (b, c; percentage atrophy 69) flexor digitorum sublimis muscle.



(a)

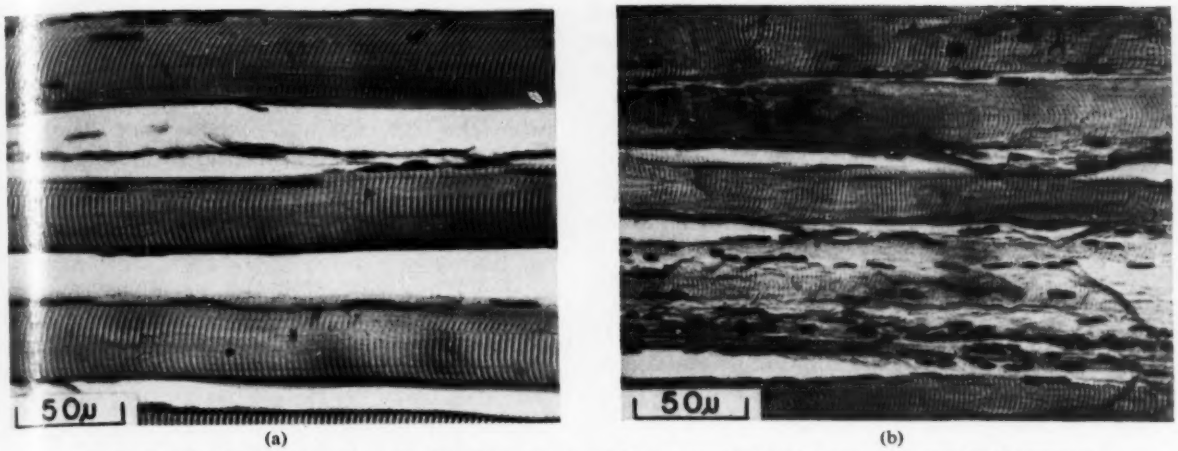


(b)



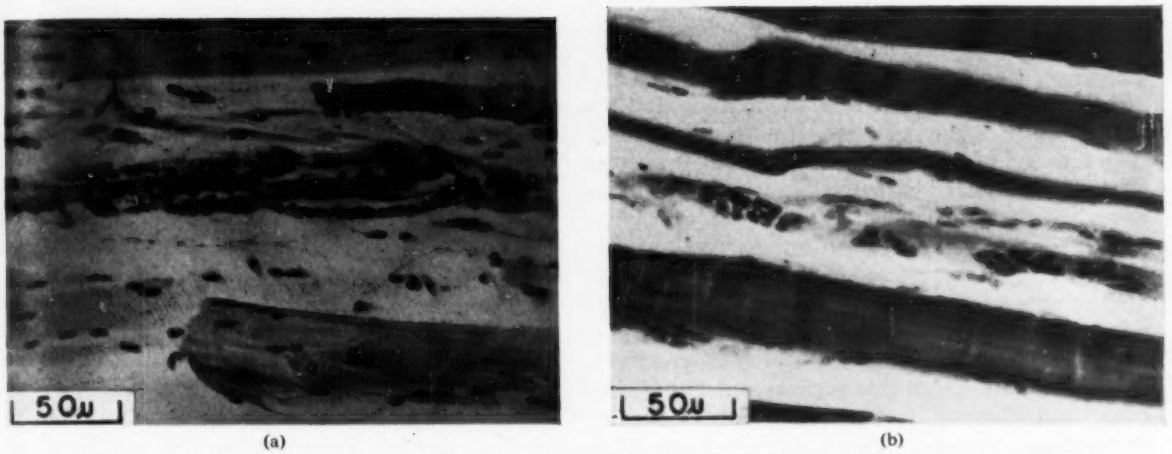
(c)

FIG. 2.—Transverse sections from the normal (a), and tenotomized (b, c; percentage atrophy 62) extensor indicis proprius muscle.



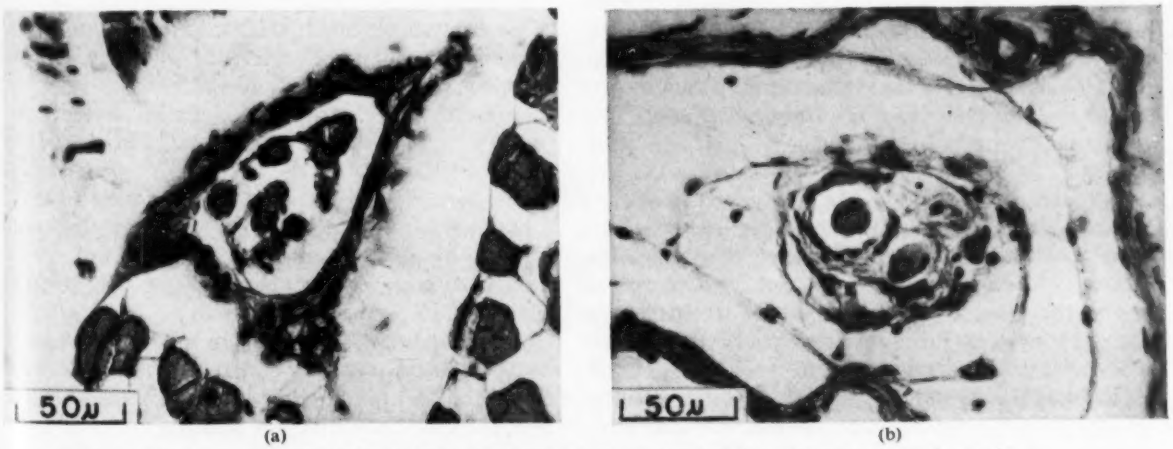
(a) (b)

FIG. 3.—Longitudinal sections of muscle fibres from the normal (a) and tenotomized (b; percentage atrophy 62) extensor pollicis longus muscle.



(a) (b)

FIG. 4.—Longitudinal sections showing nuclear aggregations in and about degenerated muscle fibres from the tenotomized extensor indicis proprius (a) and flexor digitorum sublimis (b) muscles.



(a) (b)

FIG. 5.—Transverse sections of spindles from the normal (a) and tenotomized (b) extensor carpi ulnaris muscle.

Ranson's (1930) material. Tower (1937) describes paling of the cross striation which, however, endured "to the end".

End Plates.—We are unable to state whether or not there was any reduction in the number of plates but the examination of large numbers of sections indicated that atrophied fibres carried end plates which showed no significant change in their morphology. These findings agree with those of Chor and Dolkart (1936). According to Tower (1937) "sole plate nuclei maintain their size and numbers until abruptly they disappear", though progressive failure to stain and the disorganization of neuromuscular relations with advanced atrophy were also described. We were unable to detect any signs of disintegrating plates though such evidence is unlikely to survive 20 years after amputation.

Muscle Fibre Degenération.—There was evidence of some degeneration in addition to atrophy of fibres (Figs. 1, 2, and 4). This degeneration was observed among the fibres showing the most extreme atrophy. Here thread-like fibres had fragmented into segments by a process of vacuolation and this change was accompanied by a round cell reaction. Aggregations of large, round to oval, palely staining nuclei occurred at intervals along the degenerating fibres and were interpreted as persisting muscle and end plate nuclei. Foci of degeneration were observed in the flexor digitorum sublimis, extensor pollicis longus, extensor carpi ulnaris, and extensor indicis proprius muscles. These areas of degeneration were not, however, a characteristic feature of the sections.

Smith (1928), Davenport and Ranson (1930), and Chor and Dolkart (1936) could not detect any degeneration of muscle fibres. On the other hand, Froboese (1922) reports a fatty degeneration and replacement by connective tissue while Thompson (1934) saw an occasional degenerating fibre. Tower (1937) has reported the most profound changes during which "by progressive loss of muscle substance and nuclei and paling of cross striation, muscle fibres are metamorphosed into tendon-like fibres and muscle tissue into fibrous tissue".

The Neuromuscular Spindle

Spindles could be readily identified in all the affected muscles and did not differ qualitatively from those of the normal muscles (Fig. 5). The capsule was composed of a relatively thin sheath of connective tissue which was clearly distinct from the surrounding intramuscular connective tissue. The periaxial space was patent and well defined. Each spindle contained several intrafusal fibres which were normal in appearance though some atrophy could not be excluded. There was no evidence of degeneration in any of the spindles examined.

According to Tower (1937) "the spindles share in the general fibrosis but appear otherwise unaffected" while the thin intrafusal fibres do not atrophy; in densely fibrotic and degenerating areas, however, the spindles were much altered.

Connective Tissue

It was obvious from an examination of the sections that there was a differential effect on the two chief components of the muscles, namely, the muscle fibres and supporting tissue (Figs. 1 and 2). After tenotomy the relative areas of the two, as seen in a histological section, are changed and with the atrophy of the muscle fibres there is an apparent increase in the connective tissue framework of the muscle. This effect was generalized but occurred maximally in association with the areas of extreme atrophy and muscle fibre degeneration where the connective tissue elements overshadowed the surviving muscle fibres. Thickening of the perivascular connective tissue was also well marked. The changes involved an increase in the thickness of the endomysium and perimysial septa, with duplication and reduplication of the collagen fibres between the muscle fibres and a marked increase in the nuclei of fibroblasts and small round cells. These changes were specially noticeable in the extensor indicis proprius, flexor digitorum sublimis, extensor pollicis longus, and extensor carpi ulnaris while they were relatively slight in the extensor carpi radialis longus.

In order to obtain quantitative data on the relative distribution of muscle tissue and connective tissue in the muscles the sections were analysed by a method introduced by Chalkley (1943) for "measuring directly the area ratios of components of tissues or organs under any conditions, where the various components are clearly distinguishable visually". This analysis revealed a reduction in the amount of muscle tissue and an increase in the amount of connective tissue in the affected muscles relative to one another. The next point to be determined is whether this increase is relative or real. Having obtained the area ratios for muscle and connective tissue the total weight of each in the muscle was then obtained by multiplying the weight of the whole muscle by the percentage of muscle and of connective tissue. In arriving at these values certain assumptions were made, namely:—

(*a*) That the cross section of a muscle presents a reasonably representative picture of conditions prevailing in the muscle as a whole. The ideal method would be to determine the relative areas of muscle and supporting tissue in each of a complete set of

several sections. Obviously this was not a practicable proposition in these muscles.

(b) That the relative water content of the two was the same.

With these assumptions in mind, the calculations revealed that the increase in connective tissue was relative and not absolute. There was in fact an overall reduction in the amount of connective tissue as well as of the muscle tissue, the reduction, however, being much greater in the case of the latter. The following values were obtained:

Percentage loss of muscle tissue	60 to 83	depending on the muscle
Percentage loss of connective tissue	32 to 43	

The extensor carpi radialis longus was exceptional in that it showed a 59% loss in muscle tissue and a 60% loss in connective tissue.

An "increase" in connective tissue was an outstanding feature in Krauss' (1888) and Tower's (1937) material and was also reported by Froboese (1922). Thompson (1934) saw a few areas showing marked fibrosis but Ricker (1901) and Chor and Dolkart (1936) were unable to detect any increase. According to Davenport and Ranson (1930) there was "no increase of connective tissue that can be demonstrated histologically" though "it seems possible that a change may have taken place in the character of the connective tissue without an actual increase in quantity".

Vascular Changes

There were no abnormalities in the vessels or vascular pattern in our material other than the perivascular connective tissue thickening referred to earlier. Chor and Dolkart (1936) reported normal vessels. Tower (1937) could not detect any thickening of the endothelium such as she observed after denervation, though she also observed a deposition of fibrous tissue on the outside of some vessels.

Intramuscular Nerves

Tower (1937) reported a fibrosis which enveloped but did not invade the nerve fibres which were "almost entirely intact" and Chor and Dolkart (1936) described nerve fibres which were normal in appearance. There were no abnormalities in the sections examined by us.

General

It is impossible to reconcile the findings reported in this paper with those described by Tower who concluded that

> "regardless of the condition determining disuse of muscle, whether denervation or inactivation without denervation, whether in the course of phylogenesis or in the span of individual life, the result of disuse appears to be invariant—the muscle slowly atrophies and fibrous tissue takes its place."

It is true that there were patchy areas of degeneration in some of the material examined by us but these were not a characteristic feature of the sections. On the contrary, the general outlines of the tenotomized muscles were preserved and the picture was one in which the great majority of the fibres survived with alterations in structure which did not, however, destroy those morphological features upon which the identification of muscle tissue depends. The most conspicuous change was a reduction in size and weight of the affected muscles which was reflected in a substantial atrophy of the muscle fibres, the degree of atrophy, however, varying from fibre to fibre in the same bundle and in different parts of the same muscle. The connective tissue was also reduced in amount but not to the same extent as the muscle tissue so that in the preparations the former was relatively increased in comparison with the latter. Our findings are therefore more in accord with those of Chor and Dolkart (1936) who concluded that "Disuse atrophy consists primarily of a uniform reduction of the bulk of each muscle cell. . . . This type of atrophy is associated with very simple structural changes".

A final point of interest concerns the duration of the tenotomy, namely 20 years, from which it may be inferred that the findings in this material represent the end-point of theatrophic change in human muscle.

SUMMARY

Weight loss and histological studies have been made on the tenotomized muscles of amputation stumps in man and on other muscles of which the attachments were undisturbed but the activities curtailed by the amputation.

The general outlines of the tenotomized muscles were preserved and the great majority of the fibres survived with alterations in structure which did not, however, destroy those morphological features upon which the identification of muscle tissue depends.

The affected muscles were reduced in size and weight. The extent of this atrophy was related to the amount of disuse to which the muscle was subjected. The atrophy in the tenotomized muscles varied from 39 to 69% and in the muscles of which the functions had been curtailed from 16 to 28%.

Histologically the essential change was of a simple atrophy of the muscle fibres. The weight loss was reflected in a substantial atrophy of the muscle fibres which was generalized but not uniform throughout the muscles. Some fibres suffered more than others in the same muscle and in the same fasciculus.

Patchy areas of degeneration were observed in sections of some of the muscles but these were not a characteristic feature of the sections.

The connective tissue was also reduced in amount but not to the same extent as the muscle tissue. The differential effect was such that the former was relatively increased with reference to the latter.

The neuromuscular spindles and intramuscular blood vessels and nerves appeared normal.

The duration of the tenotomy in the material investigated was one and 20 years. From this it is inferred that the findings represent the end-point of the atrophic change in human muscle after tenotomy.

References

Audova, A. (1922). *Schweiz. Arch. Neurol. Psychiat.*, **10**, 211.
Carey, E. J., Haushalter, E., Massopust, L. C., Garofalo, F., Lynch, J., Tabat, D., and Socoloff, E. (1947). *Proc. Soc. exp. Biol. (N.Y.)*, **64**, 193.
Chalkley, H. W. (1943). *J. nat. Cancer Inst.*, **4**, 47.
Chor, H., and Dolkart, R. E. (1936). *Amer. J. Physiol.*, **117**, 6.
Davenport, H. K., and Ranson, S. W. (1930). *Arch. Surg. (Chicago)*, **21**, 995.
Eccles, J. C. (1944). *J. Physiol. (Lond.)*, **103**, 253.
Fischer, E. (1941). *Proc. Soc. exp. Biol. (N.Y.)*, **47**, 277.
——, and Ramsey, V. W. (1946). *Amer. J. Physiol.*, **145**, 571.
Froboese, C. (1922). *Mitt. Grenzgeb. Med. Chir.*, **35**, 683.
Hirohasi, S. (1938). *Jap. J. med. Sci. III, Biophysics*, **5**, 367.
Knowlton, G. C., and Hines, H. M. (1940). *Amer. J. Physiol.*, **128**, 521.
Krauss, E. (1888). *Virchows Arch. path. Anat.*, **113**, 315.
Langley, J. N. (1916). *J. Physiol. (Lond.)*, **50**, 335.
—— (1917). *Ibid.*, **51**, 377.
——, and Hashimoto, M. (1918). *Ibid.*, **52**, 15.
Lippmann, R. K., and Selig, S. (1928). *Surg. Gynec. Obstet.*, **47**, 512.
Lipschütz, A., and Audova, A. (1921). *J. Physiol. (Lond.)*, **55**, 300.
Ricker, G. (1901). *Virchows Arch. path. Anat.*, **165**, 263.
Smith, N. R. (1928). *J. Anat. (Lond.)*, **62**, 238.
Solandt, D. Y., Partridge, R. C., and Hunter, J. (1943). *J. Neurophysiol.*, **6**, 17.
Thompson, T. C. (1934). *J. Bone J. Surg.*, **16**, 564.
Tower, S. S. (1937). *J. comp. Neurol.*, **67**, 241.

THE MAY (1959) ISSUE

The May (1959) issue contains the following papers:—

The Two Components of the Grasp Reflex after Ablation of Frontal Cortex in Monkeys. Geoffrey Rushworth and D. Denny-Brown.

Congenital Hydrocephalus with Defective Development of the Cerebellar Vermis (Dandy-Walker Syndrome). A. Brodal and E. Hauglie-Hanssen.

A Method for the Localization and Production of Discrete Destructive Lesions in Brain. I. R. McCaul.

The Effects of Induced Hyperthermia on Patients with Multiple Sclerosis. Dewey A. Nelson and Fletcher McDowell.

The Cholesterol and Cholesterol Ester Content of Cerebrospinal Fluid in Patients with Multiple Sclerosis and Other Neurological Diseases. Joseph B. Green, Nicholas Papadopoulos, William Cevallos, Francis M. Forster, and Walter C. Hess.

Acute Demyelinating Disease Complicating Herpes Zoster. Douglas McAlpine, Y. Kuroiwa, Y. Toyokura, and S. Araki.

Prosopagnosia. B. Bornstein and D. P. Kidron.

The Value of Leucotomy in Relation to Diagnosis. A. A. Robin.

The Effects of Meprobamite and Pentobarbitone Sodium on Sleep and Motility during Sleep: A Controlled Trial with Psychiatric Patients. J. M. Hinton and E. Marley.

Paraplegia Caused by Extraspinal Metastasis from a Uterine Fibroid. Lambert Rogers and Lewis Thomas.

Neurological Aspects of Leptospirosis. R. W. Ross Russell.

Book Reviews.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s.* 6*d.*

J. Neurol. Neurosurg. Psychiat., 1959. **22**, 175.

THE RANGE OF CONDUCTION VELOCITY IN NORMAL MOTOR NERVE FIBRES TO THE SMALL MUSCLES OF THE HAND AND FOOT

BY

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From the National Hospital, Queen Square, and the Middlesex Hospital, London

Although measurements of nerve conduction velocity in man were first made nearly a hundred years ago, the procedure was not used clinically until 1948 when Hodes, Larrabee, and German reported reduced conduction velocity in regenerating motor nerves. Later, Hodes (1949) described slow conduction in surviving nerve fibres after poliomyelitis, and more recently it has been shown that conduction may also be slow in certain localized peripheral nerve lesions (Simpson, 1956), in polyneuritis, and in peroneal muscular atrophy (Henriksen, 1956; Lambert, 1956; Gilliatt and Thomas, 1957; Gilliatt and Sears, 1958).

The use of conduction velocity measurement as a diagnostic procedure in neurology requires a knowledge of the range of values encountered in healthy individuals. Normal values for maximum conduction velocity in human peripheral nerves have already been described by Norris, Shock, and Wagman (1953) and by Henriksen (1956), but in order to obtain a control series for our own laboratory, we have estimated maximum conduction velocity in 180 normal nerves supplying the small muscles of the hands and feet. Our own results, which are in good agreement with those of previous writers, are contained in the first part of this paper.

In estimating conduction velocity, the motor nerve trunk is stimulated at two levels and the time interval between the stimulus and the onset of the muscle action potential recorded in both instances. This interval represents conduction time in the largest and most rapidly conducting motor nerve fibres stimulated, together with a further delay at the neuromuscular junction and in the muscle itself. Provided that both stimuli are supramaximal, the difference in latency of the two muscle responses is a valid estimate of conduction time in the most rapidly conducting fibres in the nerve trunk between the two points stimulated. However, conduction time in the smaller and more slowly conducting fibres of a motor nerve cannot be measured in this way as the time of onset of their muscle action potentials is obscured by the discharge of earlier units.

This point is of some clinical importance, as it is not uncommon for patients to show values for maximum conduction velocity that are slightly below the accepted normal range; in such a case the question arises as to whether this represents conduction in abnormal fibres or whether it could be due to conduction in slow normal fibres uncovered by the loss of the larger and more rapidly conducting ones.

In order to obtain some evidence on this question, we have attempted to compare the conduction times of different nerve fibres supplying a single muscle; the results of this investigation are presented in the second part of the paper.

Methods

All tests were performed in a warm room with the subject lying on a couch and covered with blankets. In a few subjects with cold hands or feet, the limbs to be tested were immersed in hot water for five or 10 minutes before the session, but no other method of controlling temperature was attempted.

In measurements of maximum conduction velocity on 77 subjects examined at the National Hospital, the stimulus was a brief condenser discharge with a time constant of 70 μsec.; for 73 subjects seen at the Middlesex Hospital, a "stanco" double-channel electromyograph was used, the stimulus being a rectangular pulse of 100 μsec. duration. In both instances the stimulus was delivered through an isolating transformer. For the stimulating cathodes, Walter type E.E.G. pad electrodes with a diameter of approximately 1 cm. were used. When stimulating the median or ulnar nerve, the distal stimulating cathode was placed over the nerve trunk at a point 2 to 3 cm. above the wrist crease; the proximal stimulus was applied 3 to 5 cm. above the elbow. The length of nerve between the two points stimulated was estimated by surface measurement and was usually between 25 and 30 cm. The anode was a plate electrode 2·5 $\times$ 5 cm. placed over the flexor surface of the forearm

or over the deltoid insertion; these anode positions were chosen for convenience and did not affect nerve conduction time.

In the legs, the distal shock was applied to the anterior or posterior tibial nerve at the level of the ankle; the proximal shock was applied to the lateral popliteal nerve at the level of the head of the fibula or to the medial popliteal nerve immediately behind the knee joint. Surface measurement between the proximal and distal electrodes usually gave a conduction distance of 30 to 40 cm. In these experiments the anode plate was situated either over the tibia itself or over the medial surface of the thigh just above the knee.

Muscle action potentials from the small muscles of the hands and feet were recorded through co-axial needle electrodes as described by Simpson (1956). In each case the position of the needle tip in the muscle was adjusted until the earliest response to a given stimulus was found and care was taken to ensure that the initial phase of the evoked potential was similar in appearance for both proximal and distal stimuli.

With the sweep of the cathode-ray tube locked to the stimulator, supramaximal shocks were applied once per second, the muscle response being amplified and displayed on a double-beam oscilloscope. The second beam was used to provide a time scale. Photographic superimposition of 10 successive responses was used by Simpson (1956) but in our own experience this was rarely necessary. Using brief shocks and a slow repetition rate, it was unusual for subjects to find the procedure unpleasant although stimulus intensity was supramaximal for motor fibres.

For each stimulating position, the time from the beginning of the stimulus artefact to the earliest deflection caused by the muscle response was measured and recorded in milliseconds. When the "stanco" electromyograph was used, the oscillograph sweep was triggered by the stimulus and measurement was made from the beginning of the trace. Conduction time for the segment of nerve between the two stimulating cathodes was then obtained by subtraction of the shorter from the longer figure and conduction velocity calculated in metres per second (m.p.s.).

Results

Maximum Conduction Velocity.—In the hand, observations were made on motor fibres to the abductor pollicis brevis, the abductor digiti minimi, and the first dorsal interosseous muscle. In the foot, the extensor digitorum brevis and abductor hallucis were examined. As in a previous study (Gilliatt and Sears, 1958), these control observations were made not only on healthy subjects working in the laboratory but also on the unaffected nerves of patients presenting isolated peripheral nerve lesions. In all, 180 observations were made on 150 subjects, no difference being found between staff and patients. The results obtained are given in Table I and in Figs. 1 and 2.

The mean values for maximum conduction velocity of the motor fibres to the small hand muscles are all closely similar and statistical comparison (t test) reveals no significant difference between them. The mean value for all three muscles taken together is 56·1 ± 4·7 m.p.s. In the lower limb, however, maximum conduction velocity is less and, moreover, the value for the fibres to the extensor digitorum brevis (49·7 m.p.s.) is appreciably greater than for the abductor hallucis (43·2 m.p.s.); this difference is statistically significant ($t = 4{\cdot}10$; $P < 0{\cdot}001$).

TABLE I

MAXIMUM CONDUCTION VELOCITY FOR MOTOR FIBRES TO SMALL MUSCLES OF HANDS AND FEET

Muscle	Number of Subjects	Conduction Velocity (m.p.s.)	
		Mean (with S.D.)	Range
Abductor pollicis brevis	25	57·2 ± 4·2	51·8 – 67·1
Abductor digiti minimi	46	56·2 ± 4·6	49·0 – 65·6
First dorsal interosseous	49	55·0 ± 4·9	46·2 – 66·2
Extensor digitorum brevis	30	49·7 ± 7·1	35·6 – 63·5
Abductor hallucis	30	43·2 ± 4·9	36·6 – 55·9

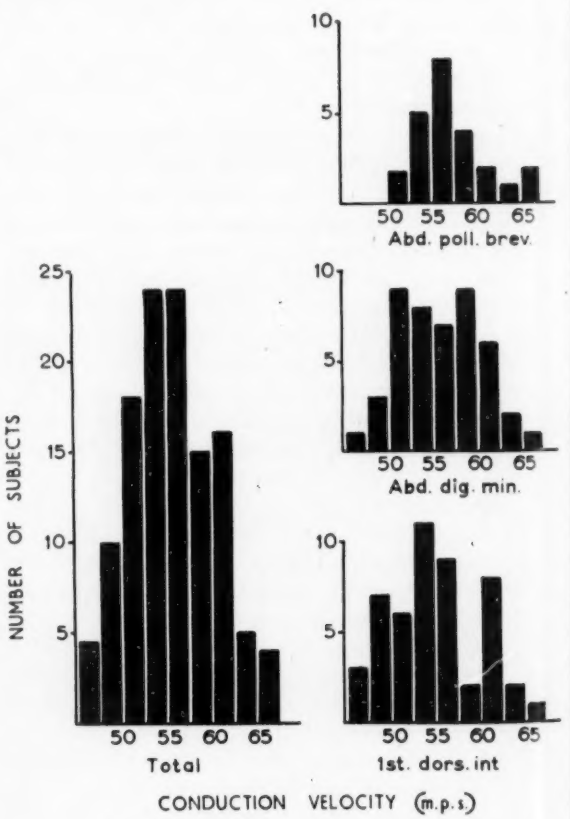

FIG. 1.—Distribution of maximum conduction velocity (in metres per second) for motor nerve fibres to the abductor digiti minimi, the first dorsal interosseous, and the abductor pollicis brevis.

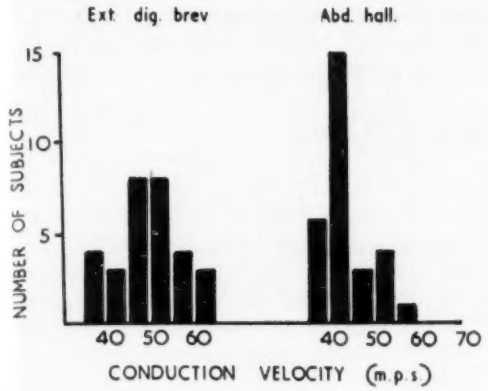

FIG. 2.—Distribution of maximum conduction velocity (in metres per second) for motor nerve fibres to the extensor digitorum brevis and the abductor hallucis.

The ages of the subjects examined are shown in Table II. Nerve conduction velocity is known to decrease in the elderly and no patients over the age of 65 were included in our series. The lower age limit was 18. From Table II it can be seen that most of the observations were on patients between the ages of 36 and 55 and that there are insufficient data from younger age groups to permit a detailed analysis of nerve conduction velocity at different ages. It is clear from Table II, however, that the differences in nerve conduction velocity between foot and hand groups cannot be explained by differences in age of the subjects tested.

TABLE II

NUMBERS OF SUBJECTS IN DIFFERENT AGE GROUPS EXAMINED

	Age Group				
	18 to 25	26 to 35	36 to 45	46 to 55	56 to 65
Abductor pollicis brevis	2	6	6	8	3
Abductor digiti minimi	3	6	15	15	7
First dorsal interosseous	2	5	20	14	8
Extensor digitorum brevis	0	6	10	13	1
Abductor hallucis	5	9	4	11	1
Total	12	32	55	61	20

Range of Conduction Velocity in Motor Fibres Supplying a Single Muscle.—Since the largest fibres in a nerve trunk have the lowest electrical threshold, a weak stimulus to the nerve is unlikely to excite small and relatively slowly conducting fibres. With a stronger stimulus the time of arrival of slowly propagated impulses at the muscle will be obscured by the discharge of earlier units. There is thus no simple method of examining the conduction rate of the slower fibres in the motor nerve trunk. (It should be pointed out that only the large motor fibres to the extrafusal muscle fibres are being considered.)

In attempting to examine the range of conduction velocity in the motor nerves to the extrafusal fibres, the most direct approach would be to compare the dispersion of the muscle action potential, recorded by surface electrodes, when the nerve is stimulated at two levels. In Fig. 4, for example, the duration of the muscle action potential of the extensor digitorum brevis is only slightly less when the motor nerve is stimulated at the ankle than when it is stimulated at the head of the fibula. This suggests that the range of conduction velocities in the motor fibres to this muscle is limited. However, this conclusion is open to objection, for Merton (1954) has shown that after electrical stimulation of a nerve trunk artificial synchronization of propagation in different muscle fibres occurs; this results in a reduction in the duration of the compound action potential.

In order to avoid this objection, it was suggested to us by Dr. Merton that if a motor nerve were stimulated proximally in the limb and the onset of the muscle response recorded in the usual way from a muscle in the hand or foot, the larger and faster motor fibres could be selectively blocked by a preceding submaximal shock to the nerve distally, thus making it possible to study the conduction time of slower fibres in isolation.

The technique is illustrated in Fig. 3, and the result of an experiment on the extensor digitorum brevis is shown in Fig. 4. The muscle action potential is recorded by surface electrodes and the test shock, S2, given to the lateral popliteal nerve at the knee, the stimulus being supramaximal. A preceding shock, S1, is applied to the nerve at the ankle a few

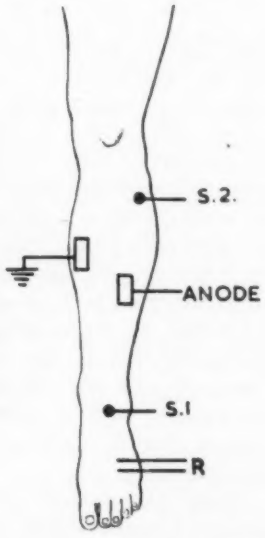

FIG. 3.—Arrangement of stimulating (S1 and S2) and recording electrodes (R) for experiments to determine the range of conduction velocity in the motor nerve fibres to the extensor digitorum brevis. A maximal stimulus (S2) is preceded by a submaximal stimulus (S1) which blocks conduction in the faster and lower threshold nerve fibres. The time of arrival of the S2 volley at the muscle can be recorded for the slower nerve fibres to the muscle.

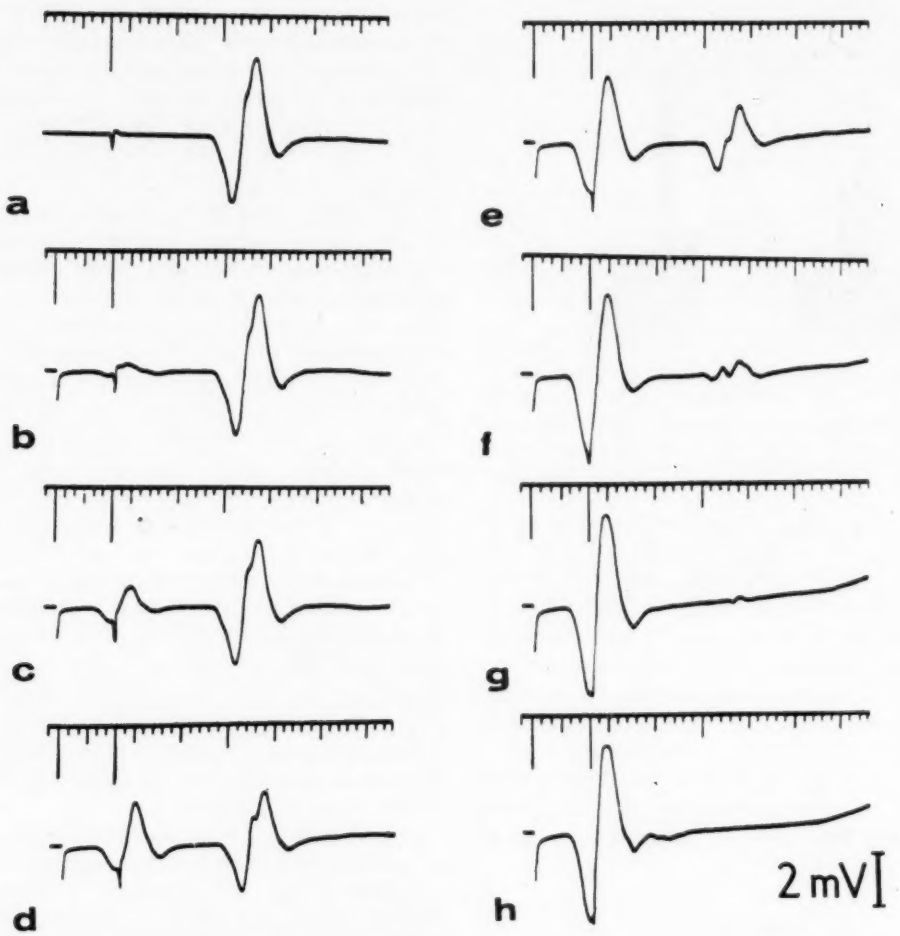

FIG. 4.—Recordings from the extensor digitorum brevis during experiments to determine the range of conduction velocity in its motor fibres. Fig. 4a shows the stimulus artefact of S2 followed by the muscle action potential. In Figs. 4b to h, S1 precedes S2 by 6 m.sec., the shock strength of S1 being increased progressively from threshold in Fig. 4b to maximal in Fig. 4h. Time scale, 1 and 5 m.sec.

milli-seconds before the test shock and, if maximal, the antidromic volley will completely extinguish the descending volley from the test shock. In the experiment shown, S1 was arranged to precede S2 by 6 m.sec. in order to obtain the maximum separation between the two stimuli, conduction time between the knee and ankle being 7 to 8 m.sec. The strength of S1 was gradually increased from zero, until the muscle response to S2 was finally extinguished. This is illustrated in Fig. 4. In the first trace (4a), the response to S2 is seen in isolation; in succeeding traces, the strength of S1 is gradually increased and the response to S2, is progressively eliminated, with a corresponding increase in its latency until in the final trace, the response to S1 alone remains.

Three experiments on the extensor digitorum brevis were performed in two subjects; in a further six experiments on four subjects the motor fibres supplying the abductor digiti minimi were examined in the same way, with surface recording electrodes placed over this muscle and stimulating electrodes over the ulnar nerve trunk just above the wrist and elbow. Similar results were obtained in all subjects and the results of two representative experiments are shown in Table III and in Fig. 5, in which the area of the muscle action potential (in response to S2), expressed as a percentage of its initial value, is plotted against the percentage increase in latency on increasing the strength of S1. The area was estimated, on camera lucida projections on to squared paper, by continuing the base line through the potential and measuring the area enclosed by deviations of the trace to either side of this. The curves for the foot and hand are closely similar, and it is of interest that the muscle action potential falls to about 10% of its

tial value with only a 15 to 20% increase in ency, although in both muscles there are a small mber of motor units with a latency of 30 to 40% low the maximum.

f it is accepted that the area of the compound scle action potential is proportional to the mber of motor units activated, a further point of rest is the form of the curves shown in Fig. 5. If nerve fibre size to these muscles were normally distributed, a reversed sigmoid curve might be expected, but curves of the form shown would be encountered if the distribution were markedly skewed. As an alternative explanation, it could be suggested that the larger fibres may contribute to a relatively greater extent to the area of the muscle action potential by possessing larger motor units. There is no decisive anatomical evidence on these points, although the latter possibility, at least, seems unlikely (see Fernand and Young, 1951). Thirdly, it is possible that the asymmetry of the curves results from muscle synchronization, as described by Merton (1954), occurring where the number of active muscle fibres is large, *i.e.*, to the left of the curve, but failing to occur when the numbers are small, *i.e.*, to the right.

TABLE III

RESULTS OF EXPERIMENTS SHOWN IN Fig. 4.

Stimulus Intensity (S1) in Volts	Latency (m.sec.)	Percentage Increase in Latency	Area of Muscle Action Potential (% of Initial Value)
Abductor digiti minimi			
0	9·0	—	100
25	9·0	—	97
30	9·2	2·2	86
35	9·8	8·9	37
37·5	10·0	11·1	20
40	11·8	31·1	3
Extensor digitorum brevis			
0	10·8	—	100
49	10·9	0·9	97
53	11·0	1·9	88
57	11·0	1·9	66
62	12·1	12·0	36
67	12·5	15·7	13
90	15·0	39·1	1

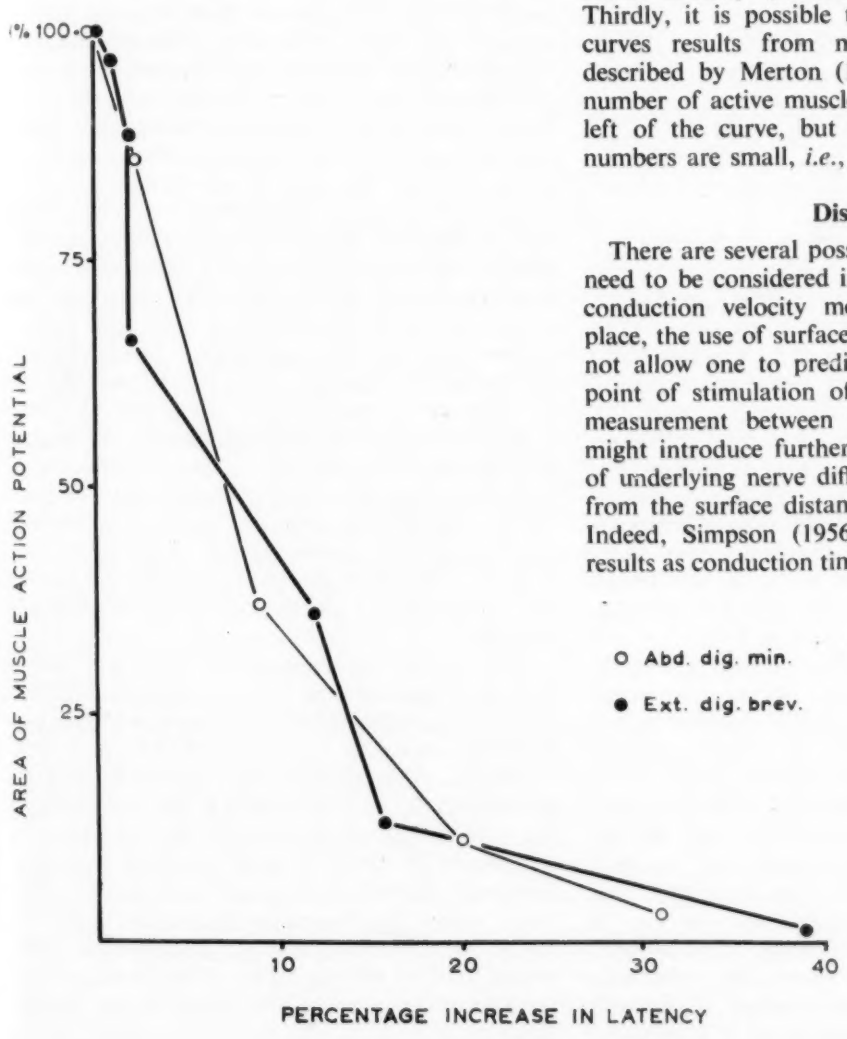

FIG. 5.—Relationship between area of muscle action potential evoked by S2 and latency of response. Results for the abductor digiti minimi and the extensor digitorum brevis in a single subject.

Discussion

There are several possible sources of error which need to be considered in interpreting human nerve conduction velocity measurements. In the first place, the use of surface stimulating electrodes does not allow one to predict with accuracy the exact point of stimulation of the nerve itself. Surface measurement between two stimulating electrodes might introduce further errors if the actual length of underlying nerve differed to any marked extent from the surface distance between the two points. Indeed, Simpson (1956) preferred to present his results as conduction times to avoid figures based on

surface measurement. These objections are discussed in detail by both Carpendale (1956) and Henriksen (1956), who compared motor nerve conduction times during percutaneous stimulation using cathodes of different sizes and in different positions over the nerve trunk. These authors concluded that small lateral movements of the stimulating electrode did not produce significant changes in the latency of the muscle response and that with cathode diameters of up to 2 cm. stimulation appeared to occur under the centre of the electrode. In addition, Carpendale compared the actual length of median and ulnar nerves found on dissection of the forearm with the results of surface measurements in four cadavers and concluded that the errors introduced in this way were of little importance.

A more serious difficulty is that due to differences in temperature. In our series, it is likely that temperature variation accounted for much of the observed variation between different individuals, and further experiments on this point are clearly required. In the present series, however, we have deliberately accepted variations due to uncontrolled temperature in order that the results might be directly applicable to patients seen in routine electrodiagnostic clinics where elaborate temperature control is impracticable.

The only published investigation of the effect of temperature on conduction velocity in man is that of Henriksen (1956) who measured conduction velocity in the motor fibres of the ulnar nerve in the forearm with the arm immersed in a water bath. Temperature was recorded by a thermistor buried to a depth of 2 cm. in the proximal third of the forearm near the course of the nerve and varied between 29° and 38°. The mean alteration in conduction velocity was 2·4 m.p.s. per degree change in temperature. Henriksen also measured temperature during recordings made under similar conditions to those employed in our series and found that muscle temperatures for different subjects generally varied between 34° and 36·5°C.

The use of co-axial needles instead of surface recording electrodes is open to the theoretical objection that the needle electrode samples only a proportion of the motor units in a muscle, a proportion which might not be representative of the muscle as a whole. Among previous writers, Hodes, Wagman, Carpendale and Henriksen used surface electrodes, whereas Simpson preferred co-axial needles. Our own experience does not suggest that significant errors are introduced by the use of needle electrodes, at any rate in the small muscles that we have examined, and needle electrodes have clear advantages in the examination of patients with nerve lesions in that they make it possible to measure nerve conduction velocity simply and rapidly after sampling the spontaneous and voluntary activity of a paretic muscle. Furthermore, the restricted area from which the co-axial needle records is a great advantage when paretic and unaffected muscles are in close proximity. For example, during stimulation of the ulnar nerve in patients with lesions of the deep branch in the hand, the delayed response of a few surviving units in the interossei may be completely obscured in surface records by the response of unaffected hypothenar muscles. With a co-axial needle, even a single surviving unit in an affected muscle can be localized by exploration during voluntary contraction and then observed in isolation during nerve stimulation.

While our results show no significant difference in maximum conduction velocity of motor fibres to the abductor digiti minimi, the abductor pollicis brevis, and the first dorsal interosseous of the hand, the differences in velocity we have observed between the hand and foot and between fibres supplying the extensor digitorum brevis and the abductor hallucis call for comment. It is possible that the lower values obtained in the leg as compared with the arm may be accounted for in terms of a temperature effect, although this has not been tested. However, a temperature effect is unlikely to explain the disparity between the two muscles in the foot. The segments of the anterior and posterior tibial nerves over which the recordings were made are both deeply buried in muscle and a difference between the two nerves is thus improbable. In searching for an alternative explanation it will be recalled that the diameter of the anterior root fibres is greatest at the centre of the lumbar enlargement, diminishing progressively on either side of this but particularly caudally (Häggqvist, 1937; Gentele and Swensson, 1941). Since the abductor hallucis receives its innervation from more caudal segments (S1, S2) than the extensor digitorum brevis (L4, L5, S1), the fibres supplying it are thus likely to be of smaller diameter.

The scatter of conduction velocities to the abductor digiti minimi and the extensor digitorum brevis in a single subject indicates that the majority of fibres conduct at a rate within 15 to 20% of the maximum, although the lower limit of velocity may be as much as 35 to 40% below the maximum. In the rabbit, the distal muscles in the limbs are innervated by fibres of small diameter and with a restricted size range (Fernand and Young, 1951), and it seems likely that this observation is generally applicable. If this is also the situation in man, it would account for the relatively restricted range of conduction velocity in the motor nerve fibres to these muscles.

t is of interest to relate these findings to those ol ained in patients with lower motor neurone le ons. Conduction velocity in surviving fibres af er anterior poliomyelitis or in motor neurone di ease may be reduced (Hodes, 1949; Henriksen, 19 6) but values more than 30% below normal ha ve not been recorded. This degree of slowing co ld well be accounted for in terms of conduction in surviving slow normal fibres. On the other hand, so ne patients with polyneuritis and peroneal m scular atrophy may show extremely low values for nerve conduction velocity, at times below 10 metres per second. This clearly cannot be explained in terms of slow normal surviving fibres and must mean abnormal nerve function. Whether this depends upon structural or upon metabolic alterations, or upon both, has not yet been ascertained.

Summary

Conduction velocity in the fastest motor nerve fibres to the small muscles of the hand and foot was calculated for a series of normal nerves, measurements being made for fibres to the abductor pollicis brevis, the abductor digiti minimi, and the first dorsal interosseous muscle in the hand, and the extensor digitorum brevis and abductor hallucis in the foot. There was no significant difference between the hand muscles, the mean value obtained being 56·1 ± 4·7 m.p.s. The values obtained for the foot were less, being 49·7 ± 7·1 m.p.s. for the extensor digitorum brevis and 43·2 ± 4·9 m.p.s. for the abductor hallucis, the difference between these two muscles being statistically significant.

A method is described for measuring conduction velocity for the slower motor fibres to a muscle, and observations on the abductor digiti minimi and the extensor digitorum brevis indicate that there are motor fibres supplying these muscles with a conduction velocity between 30% and 40% below the maximum. The significance of this finding is discussed.

We wish to thank Dr. W. A. Cobb and Dr. G. D. Dawson for helpful criticism and advice, and Mr. H. B. Morton for technical assistance.

References

Carpendale, M. T. F. (1956). M.S. (Phys. Med.) Thesis, Univ. of Minnesota.
Fernand, V. S. V., and Young, J. Z. (1951). *Proc. roy. Soc. B.*, **139**, 38.
Gentele, H., and Swensson, Å. (1941). *Z. mikr.-anat. Forsch.*, **50**, 190.
Gilliatt, R. W., and Sears, T. A. (1958). *J. Neurol. Neurosurg. Psychiat.*, **21**, 109.
—— and Thomas, P. K. (1957). *Ann. phys. Med.*, **4**, 104.
Häggqvist, G. (1937). *Z. mikr.-anat. Forsch.*, **42**, 33.
Henriksen, J. D. (1956). M.S. (Phys. Med.) Thesis. Univ. of Minnesota.
Hodes, R. (1949). *J. Neurophysiol.* **12**, 257.
——, Larrabee, M. G., and German, W. (1948). *Arch. Neurol. Psychiat. (Chicago)*, **60**, 340.
Lambert, E. H. (1956). In *Clinical Examinations in Neurology*, p. 313. Saunders, Philadelphia.
Merton, P. A. (1954). *J. Physiol. (Lond.)*, **124**, 311.
Norris, A. H., Shock, N. W., and Wagman, I. H. (1953). *J. appl. Physiol.*, **5**, 589.
Simpson, J. A. (1956). *J. Neurol. Neurosurg. Psychiat.*, **19**, 275.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 182.

A CLINICAL AND EXPERIMENTAL STUDY OF THE EFFECTS OF EXERCISE ON MOTOR WEAKNESS IN NEUROLOGICAL DISEASE

BY

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Muscular weakness is a common neurological symptom which may result from a primary muscular disorder but is more frequently due to interference with the innervation of the muscles. Often there is no specific therapy for the disease responsible and it is necessary to decide on appropriate treatment for the affected muscles, in particular whether they should be rested or given exercise. If exercise is indicated it is important to know the most effective method of carrying it out.

The effect of a programme of exercise given to a group of neurological patients was studied by making quantitative measurements of muscle strength. The same routine of exercise was also applied to a group of healthy volunteers. A smaller group of patients carried out additional exercises designed to produce severe fatigue and the effects of this were measured.

Material and Methods

The biceps and triceps of the upper limb were selected for study as their strength can be measured comparatively easily. Patients with weakness of either of these muscles were studied if they were available for sufficient time and could cooperate in the experiments. All patients admitted over a period of two years to the Neurological Unit at the Northern General Hospital who satisfied these conditions were included.

The measurements of muscle strength were made with a dynamometer designed to register the isometric tension of the biceps or triceps. It consists of a duralumin lever which rises from a spindle on a wooden board. The patient lay with the upper arm resting on the board and the elbow flexed to 90° so that he was able either to push or pull with the wrist against a handle at the upper end of the lever. This movement was resisted by a spring and registered by a pointer on a scale. At the beginning of each experiment the scale was calibrated in pounds with a spring balance. A tension of 30 lb. corresponded with a movement of the wrist of about 3 cm.

For certain purposes a modified version was used. A similar lever with a handle deflected a spring steel bar to which it was attached at its lower end, the steel bar replacing the spring as the load. Resistance strain gauges cemented to the spring steel bar formed two sides of a Wheatstone bridge circuit fed by an A.C. voltage and kept in balance when no force was applied to the lever. The out-of-balance voltage, which is directly proportional to the deflecting force, was amplified and recorded by a pen recorder, so that a permanent record of muscle tension was obtained. It was calibrated in pounds with a spring balance and very powerful pulls produced a movement of the handle of only a few millimetres.

This apparatus was used to make measurements of muscular strength and to carry out training sessions of isometric exercise. A training session consisted of 30 maximal isometric contractions carried out at 30-second or one-minute intervals (after Darcus, 1956). The strength of the subject each day was taken as the mean of the first five contractions carried out. The percentage alteration in strength was calculated from the difference between the means of the first five observations made in each of the first three and each of the last three training sessions and also from the regression for the means of the first five observations of each of the training sessions. Measurements with the two dynamometers are closely comparable but in general the spring dynamometer was used except where a permanent written record of a contraction was necessary.

Simultaneous measurements were made of the isometric tension of the biceps or triceps and the integrated action potentials obtained from surface electrodes. The electrodes were silver discs of 1 cm. diameter placed 3 cm. apart on the belly of the muscle. The action potentials were amplified and fed into an integrator circuit which first made them unipolar and then applied them to a circuit which gave off pulses at a rate proportional to the mean voltage of the electromyogram (Bates and Cooper, 1954). These pulses were recorded by a pen recorder alongside a simultaneous record of the isometric tension. The electromyogram was calibrated in millivolts by passing sine waves of known voltage through the system.

A small group of patients was given weight lifting exercises. A heavy weight was lifted from waist to shoulder level repeatedly till the subject could no longer raise it. After a short rest the procedure would continue. The sessions lasted up to an hour and were designed to investigate the effects of fatigue.

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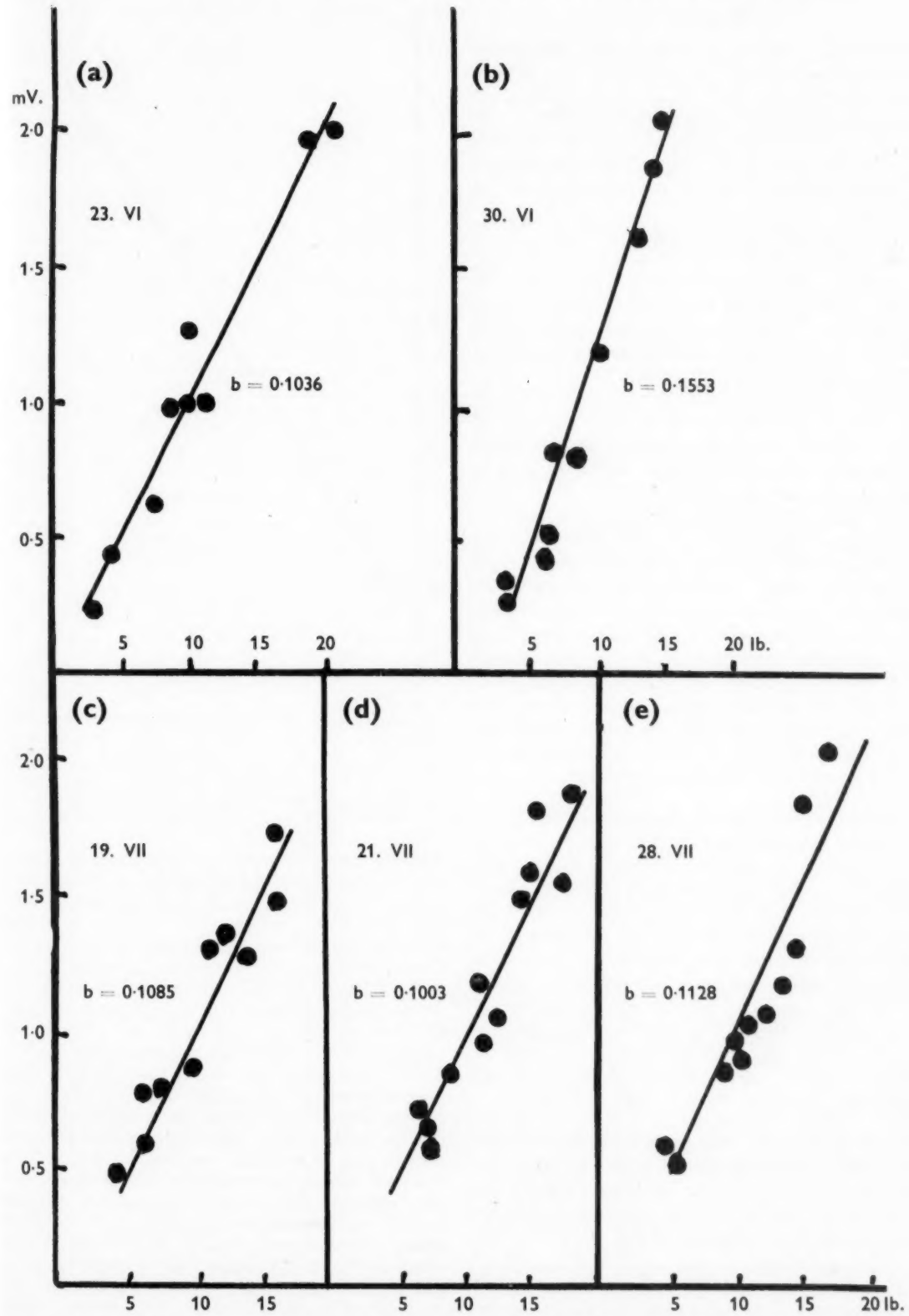

FIG. 1.—Relationship between voltage and tension of left triceps of Subject M.F.L. on five different occasions. For curve (a) regression equation is $Y = 0{\cdot}1036X - 0{\cdot}0200$. Slope of curve is represented by regression coefficient b for which the 95% confidence limits are $\pm 0{\cdot}01606$ giving a range of 0·0876 to 0·1169. The regression coefficients for all the other curves except curve (b) lie within these limits. The correlation coefficient of curve (a) with a straight line is 0·9849.

Results

Relationship between Tension and Integrated Electromyogram.—Simultaneous records during graded contractions were made of the isometric tension and the integrated action potentials of the biceps or triceps muscles of all the healthy volunteers and 14 of the patients in this series. The tension (lb.) was plotted against the mean voltage of the E.M.G. (mV.).

In each instance an increase in tension corresponded with an increase in voltage recorded from the muscle. The relationship between the two variables showed a high degree of correlation with a straight line (Fig. 1). The slope of the curve relating tension to mean voltage varied according to the conditions of the experiment, in particular the position of the electrodes and their distance apart. It also depended on the state of the muscle, and the observation of Edwards and Lippold (1956), that the slope of the curve alters when the muscle is fatigued, was confirmed repeatedly.

The relationship between voltage and tension of a muscle was determined on different occasions separated by intervals of up to several weeks. Care was taken to place the electrodes on the same position on the muscle (marking the site between experiments with adhesive tape) and to reproduce the experimental conditions as closely as possible. Fig. 1 shows the result of one such experiment. The slopes of the regression for each curve are similar. Fig. 2 shows the effect of a trick movement in a subject who would use his shoulder muscles to assist his triceps in a maximal contraction.

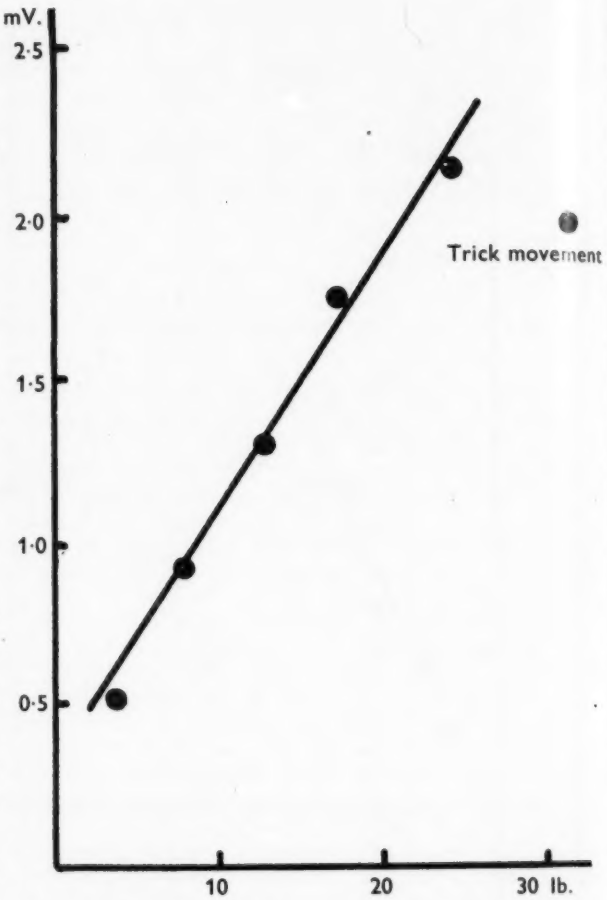

FIG. 2.—Voltage tension curve from Case 23 showing trick movement assisting left triceps muscle. A thrust of 30 lb. is associated with the same voltage from the triceps muscle as one of 24 lb. because the additional force is derived from the shoulder muscles.

Exercise Experiments on Healthy Individuals.—The range of normal values for the present technique was determined in six normal subjects using the isometric training sessions described above (Table 1).

Subjects L.F. and M.N. had approximately six training sessions per week whereas the others had exercise three or four times weekly. In each case there was a highly significant progressive improvement in the maximum tension developed, which became evident during the first nine sessions of exercise. Three of the subjects continued for 25 sessions, at the end of which improvement was still taking place (Fig. 3).

Disease of Muscle.—Six patients with weakness attributable to muscular disease were studied. The results of isometric exercise in these patients are summarized in Table I but it is necessary to consider the individual cases in greater detail.

Case 1 (MN 1667).—A boy, aged 16, with facio-scapulo-humeral muscular dystrophy carried out 75 sessions of isometric exercise with his left biceps (Fig. 4). After 10 sessions the muscle was less readily fatigued as there was a smaller fall in tension at the end of each session. After 19 sessions there was an increase in maximal voluntary tension which became progressively larger during the next 30 sessions. During the last 25 sessions the strength of the muscle declined. In the last fortnight of training he carried out weight-lifting sessions which produced severe fatigue and made the muscles sore for several days. During this period there was no significant change in the rate of deterioration.

The right biceps was weaker than the left. Regular isometric measurements of the strength of the arm (mean of five pulls) were made and during the first month there was no change. A weight-lifting programme was then started and 49 sessions were carried out. Strength increased during the first 25 sessions but after that there was little change. These exercises produced considerable fatigue but were less strenuous than the weight-lifting exercises carried out by the left arm.

Measurements of strength with this patient were made difficult by the fact that the brachio-radialis muscles were powerful and assisted the weak biceps to flex the

TABLE I

EFFECTS OF ISOMETRIC EXERCISE

Subject	Age	Diagnosis	Muscle Exercise	No. of Sessions	Maximum Tension		Effect of Exercise	
					1st Mean (lb.)	2nd Mean (lb.)	Change of Mean Maximum Tension (%)*	Change of Regression (%)†
Group 1: Healthy Subjects								
M. L. (F)	28	—	R. biceps	25	33·6	53·4	+59 (0·001)*	+53 (0·001)†
L. (F)	21	—	R. biceps	25	28·7	41·3	+45 (0·001)	+52 (0·001)
D. L. (M)	24	—	R. triceps	25	38·6	53·1	+38 (0·001)	+36 (0·001)
D. (F)	25	—	L. biceps	16	33·3	41·5	+25 (0·001)	+28 (0·001)
M. (F)	21	—	L. biceps	18	37·6	48·5	+29 (0·001)	+27 (0·001)
R. (M)	26	—	L. biceps	12	52·9	61·1	+16 (0·001)	+18 (0·001)
Group 2: Disorders of Muscle								
Case 1 (M)	16	Muscular dystrophy	L. biceps	1st 25	15·2	16·9	+11 (0·001)	+15 (0·01)
				2nd 25	16·9	19·5	+15 (0·001)	+13 (0·01)
				3rd 25	18·8	16·5	−12 (0·001)	−14 (0·001)
			R. biceps	1st 25	10·4	9·3	−11	
			(weight	2nd 25	8·9	10·8	+21 (0·001)	+19 (0·05)
			lifting)	3rd 25	11·7	11·5	− 2	
Case 2 (M)	64	Muscular dystrophy	R. biceps	9	13·4	13·4	nil	nil
Case 3 (F)	25	Polymyositis	R. biceps	1st 16	9·3	10·2	+10 (0·05)	+14 (0·10)
				2nd 15	6·9	9·6	+39 (0·001)	+55 (0·001)
Case 4 (F)	57	Polymyositis	R. triceps	21	7·8	9·3	+20 (0·001)	+23 (0·01)
Case 5 (F)	21	Polymyositis	L. biceps	1st 25	16·8	28·4	+70 (0·001)	+59 (0·001)
Group 3: Disease of Anterior Horn Cells and Pyramidal Tracts								
Case 7 (M)	70	Motor neurone disease	R. triceps	21	14·4	21·6	+47 (0·001)	+49 (0·001)
			L. biceps	11	12·4	12·1	− 2	
Case 8 (M)	46	Motor neurone disease	L. triceps	12	10·9	16·1	+48 (0·001)	+66 (0·01)
			R. triceps	15	12·2	15·6	+28 (0·001)	+34 (0·05)
			L. biceps		No measurable effect			
			R. biceps		No measurable effect			
Case 9 (F)	35	Syringomyelia	R. biceps	1st 25	5·9	7·6	+30 (0·001)	+40 (0·001)
				2nd 10	7·1	7·2	+ 1	
			L. biceps	17	15·0	15·4	+ 2	
Case 10 (M)	67	Motor neurone disease	R. triceps	18	8·7	8·7	nil	nil
Case 11 (F)	57	Motor neurone disease	R. biceps	17	3·5	3·2	− 8	
Case 12 (F)	57	Motor neurone disease	L. biceps	18	21·0	22·0	+ 5	
Case 13 (F)	61	Motor neurone disease	L. biceps	15	9·8	9·0	− 8	
Group 4: Demyelinating Disease								
Case 14 (F)	28	Multiple sclerosis	R. triceps	17	15·1	27·2	+80 (0·001)	+74 (0·001)
Case 15 (F)	61	Multiple sclerosis	L. biceps	20	2·6	3·4	+31 (N.S.)	+24 (N.S.)
Case 16 (F)	41	Multiple sclerosis	R. biceps	17	6·3	6·9	+11 (N.S.)	+26 (N.S.)
Case 17 (F)	35	Multiple sclerosis	L. biceps	14	17·9	10·6	−40 (0·001)	−40 (0·01)
Case 18 (M)	60	Multiple sclerosis	L. triceps	12	10·8	10·7	− 1	
Case 19 (M)	33	Multiple sclerosis	R. triceps	5	—	—	No change	
Case 20 (M)	34	Multiple sclerosis	L. triceps	4			+73	
Group 5: Miscellaneous Cases								
Case 22 (M)	34	Cervical p.i.d.	R. triceps	1st 9	8·5	11·9	+40 (0·001)	+57 (0·001)
				2nd 9	15·7	23·5	+50 (0·001)	+50 (0·001)
Case 23 (M)	71	Cervical root lesion	L. triceps	1st 25	11·5	15·7	+36 (0·001)	+56 (0·001)
				2nd 25	15·3	19·6	+28	
				3rd 18	19·7	19·4	−2	
Case 24 (M)	53	Cervical root lesion	R. triceps	11	12·4	18·1	+46 (0·001)	+59 (0·001)
Case 25 (M)	45	Cervical spondylosis	L. biceps	11	36·7	43·9	+20 (0·001)	+27 (0·001)
Case 26 (F)	25	Poliomyelitis	R. triceps	1st 25	6·1	9·4	+54 (0·001)	+62 (0·001)
				2nd 21	9·2	13·0	+42	
				3rd 16	13·2	15·9	+21	
Case 27 (M)	41	Brachial neuritis	L. biceps	8	17·3	23·9	+39 (0·001)	+47 (0·05)
Case 28 (M)	58	Cerebral thrombosis	R. biceps	9	17·2	26·0	+47 (0·001)	+70 (0·01)
Case 29 (F)	52	Cerebral thrombosis	R. biceps	22	11·8	8·4	−29	

*Significance of difference between means assessed by t test. †Significance of variance ratio assessed by F test.
N.S. = Not significant.

elbow. Repeated girth measurements of the upper arm, however, showed his increase in strength to be accompanied by an increase in girth around the biceps and his deterioration by a decrease in girth.

Twenty-one months later the left biceps was one third as strong as initially. The right biceps became only slightly weaker than when he was first seen.

Case 2 (MN 1934).—A man, aged 64, with facio-scapulo-humeral muscular dystrophy carried out nine sessions of isometric exercise with the right biceps with no effect.

Case 3 (MN 1259).—A woman, aged 25, had polymyositis confirmed by biopsy and electromyography. She was under observation for three years and had an episode of respiratory failure when she required intermittent positive pressure respiration.

Her courses of isometric exercise for the right biceps were separated by nine months. The first was of 16 sessions, and the small increase in strength observed was not evident until after the ninth session when she started to take prednisolone. Her strength continued to increase during the three weeks following the exercise when she

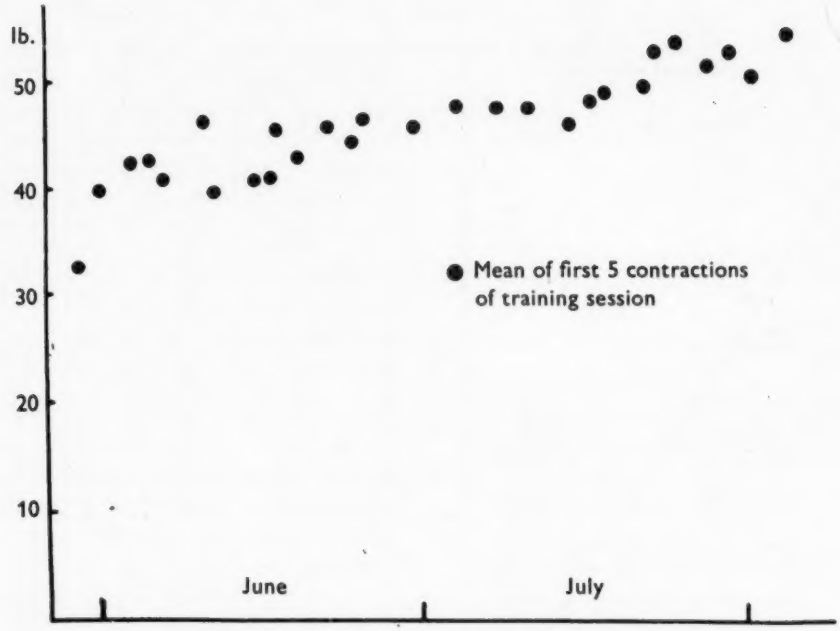

FIG. 3.—The effect of training on the strength of the triceps of a normal subject, D.M.

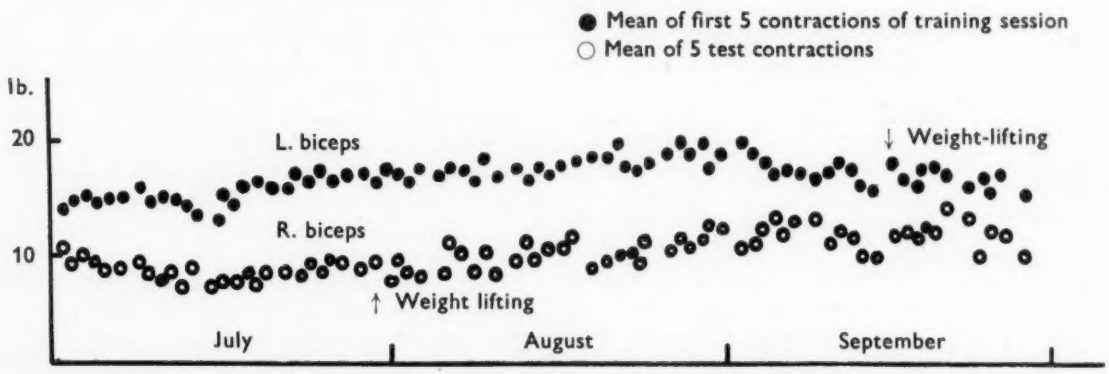

FIG. 4.—The effect of training on Case 1 (muscular dystrophy).

was still taking prednisolone. Her second course of 15 sessions was during recovery from relapse following influenza, when she was again having steroid therapy. A marked improvement occurred in the limb exercised. The other arm improved more slowly but six weeks later there was no difference in strength between the two biceps muscles.

Two things had an adverse effect on her general condition and muscle power. Her three most serious relapses were following febrile illnesses, successively glandular fever, pyelitis, and influenza. Secondly any circumstance that confined her to bed resulted in a loss of strength which would recover rapidly with physiotherapy.

Case 4 (*MN 2189*).—A woman, aged 57, had weakness of the shoulder girdle and upper arms, as a result of polymyositis. The strength of the right triceps was slightly increased during 21 sessions of isometric exercise. It was not evident until after the tenth session when she started to take prednisolone. After discharge from hospital there was a steady deterioration in strength and general condition and she died nine months later.

Case 5 (*MN 1714*).—A woman, aged 21, had a proximal weakness of all four limbs which had developed gradually over three and a half years. Her condition ran a fluctuating course and a diagnosis of polymyositis was made although histological proof was not obtained.

She carried out 70 sessions of isometric exercise with the left biceps over five months. Measurements were made of the strength of the right biceps and both triceps muscles. The striking change in the strength of the left biceps corresponded closely with improvement in those muscles which were not exercised (Fig. 5). Although

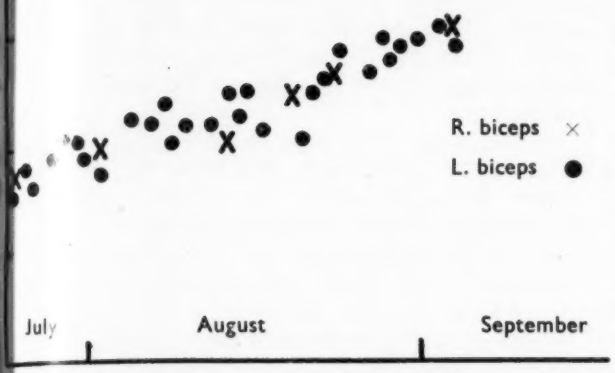

FIG. 5.—The effect of training on the left biceps of Case 5 (polymyositis) showing the corresponding changes in the contralateral muscle.

improvement began before she started steroid therapy, it reached its peak during a course of prednisolone given at this time.

When carrying out a training session her strength tended to fall off towards the end of the session. She also showed a delay in the build up of a contraction so that on a maximal voluntary effort she would take 5 to 7 sec. to attain a maximal tension compared with the normal figure of 0·5 to 1·0 sec. This has not been observed in other patients with polymyositis or with myasthenia gravis (Simpson and Lenman, 1959).

Case 6 (*MN 3119*).—A man, aged 50, had dystrophia myotonica and his arms had begun to weaken. On six days he carried out weight-lifting sessions with the left arm strenuous enough to cause prolonged fatigue. The longest of these lasted one hour and five minutes and in it he lifted 7 lb. from waist to shoulder level 339 times. The strength of the biceps was measured repeatedly and during the five weeks he was in hospital no change was noted.

Five cases of muscular disease showed an increase in strength with exercise but in four it could have been due to other treatment or to spontaneous recovery. The improvement in Case 1 was apparently a true training effect, but it was slower than that seen in normal subjects and it was vitiated by the subsequent course of the disease. No adverse effects from fatigue were noted, but, on the contrary, with Case 3 any period of enforced rest in bed was followed by a deterioration.

Degenerative Disease of Anterior Horn Cells and Pyramidal Tracts.—This group includes six cases of motor neurone disease and one of syringomyelia, and the results of isometric exercise are summarized in Table 1.

Case 7 (*MN 2103*).—A man, aged 70, had weakness of all four limbs due to motor neurone disease. During a course of 20 sessions of isometric exercise the strength of the right triceps increased by 45% (Fig. 6a). Three months later all his muscles were weaker and no change in strength was recorded during 11 sessions of isometric exercise with the left biceps (Fig. 6b). He next performed weight-lifting exercises with the left arm which were made progressively more strenuous until he was carrying out several times daily a session severe enough to cause prolonged aching of the arm. Isometric measurements made repeatedly on the biceps showed no change in strength. After leaving hospital his condition gradually deteriorated and he died three months later.

Case 8 (*MN 339*).—A man, aged 46, had a 10-year history but the clinical picture was that of motor neurone

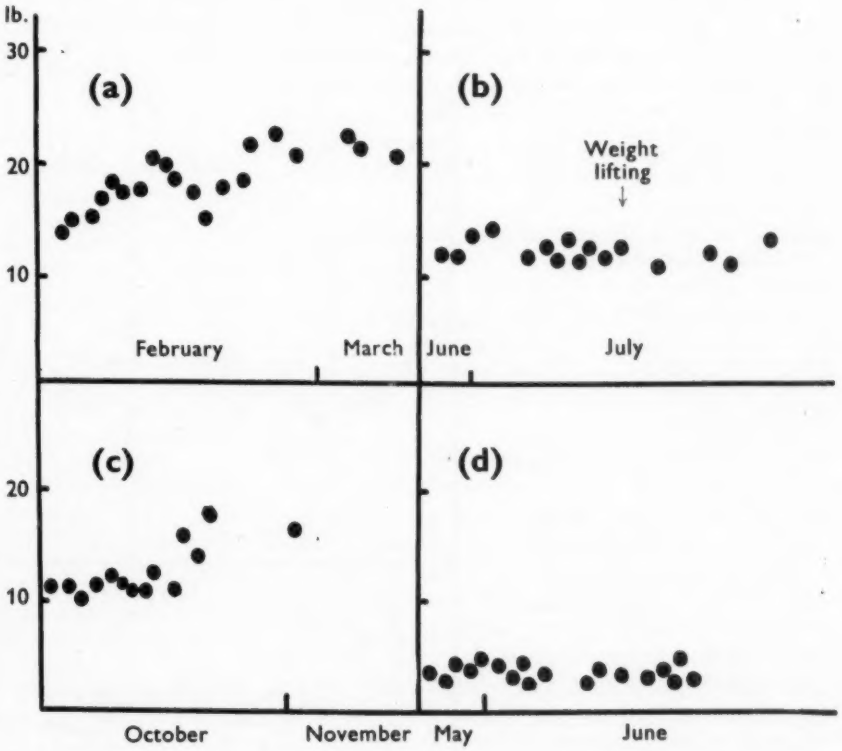

FIG. 6.—The effect of training on four muscles in patients with motor neurone disease. (*a*) Right triceps of Case 7. (*b*) Left biceps of Case 7. (*c*) Left triceps of Case 8. (*d*) Right triceps of Case 11.

disease. He had a pseudo bulbar palsy with weakness of all four limbs, marked wasting of the hands and arms, and widespread fasciculation.

He carried out a series of isometric sessions, each of 30 contractions, at one-minute intervals first with the left (Fig. 6c) and then with the right triceps. In each case there was an increase in strength which was of value as it enabled him to push himself from the lying to the sitting posture and so rise from his bed unaided. He found the exercise sessions fatiguing and after them his arm would ache for 30 to 45 minutes. During a session the maximum tension would fall by 25%. Soon after he started the exercises he noticed fasciculation in the triceps. This fasciculation, which was particularly coarse, involving the contraction of quite large bundles of fibres, was most marked at the end of an exercise session.

The biceps muscles were so weak that he found it difficult to flex his arms against gravity. Each biceps was given a course of isometric exercises but no improvement occurred.

Rest in bed affected him adversely. This he often noticed when he had a cold and on one occasion it was necessary to admit him to hospital for physiotherapy after two weeks in bed following an appendicectomy.

Case 9 (MN 1068).—A woman, aged 37, who had weak arms as a result of syringomyelia attended two to three times weekly over several months. She carried out 35 sessions of isometric exercise with the right biceps and an increase in strength of about 30% was recorded, most of it quite early. The exercises produced little fatigue and frequently at the end of a session she would record stronger contractions than at the start. At the end of her fifth session she was reaching tensions equal to those she attained at the start of her twenty-first session. She next carried out seven sessions of weight-lifting exercise over a month. These produced a sensation of fatigue in the arm but there was no further increase in strength. Subsequently strength reverted to its original level.

Her left arm was stronger than the right and a course of 17 sessions of isometric exercise carried out with the left biceps was without effect.

The remaining four patients in this group, Case 10 (MN 2333), Case 11 (MN 2338) (Fig. 6d), Case 12 (MN 2801), and Case 13, had motor neurone disease. They each carried out isometric exercise with a weak upper limb muscle with no effect. Case 13 (MN 3229), a woman, aged 61, in addition carried out six sessions of weight-lifting exercises with the right biceps during eight days. These resulted in prolonged aching of the muscle but had no effect on her strength.

All the cases in this group were right handed. Cases 7, 12, and 13 were affected earlier or more severely on the left side. Cases 8, 10, and 11 were affected more severely on the right side. Case 9 was worse on the right side at the time she came under study but for 10 years previously the left upper limb had also been affected.

In this group of seven patients 12 muscles were exercised systematically. Four of the muscles exercised became stronger. With Case 8 the isometric exercises produced moderate fatigue. Cases 7, 9, and 13 carried out weight-lifting exercises designed to produce fatigue. No adverse effects were recorded following this treatment.

Demyelinating Disease.—Of the eight cases studied seven carried out isometric exercises and the results of these are summarized on Table I.

Cases 14 (MN 1653) and 20 (MN 2267) showed a more rapid increase in strength than any observed in healthy individuals, which corresponded with a change in other muscles not exercised and with a clinical improvement. Cases 15, 16 (MN 1950), 17 (MN 2747), 18, and 19 (MN 1064), were at a stage

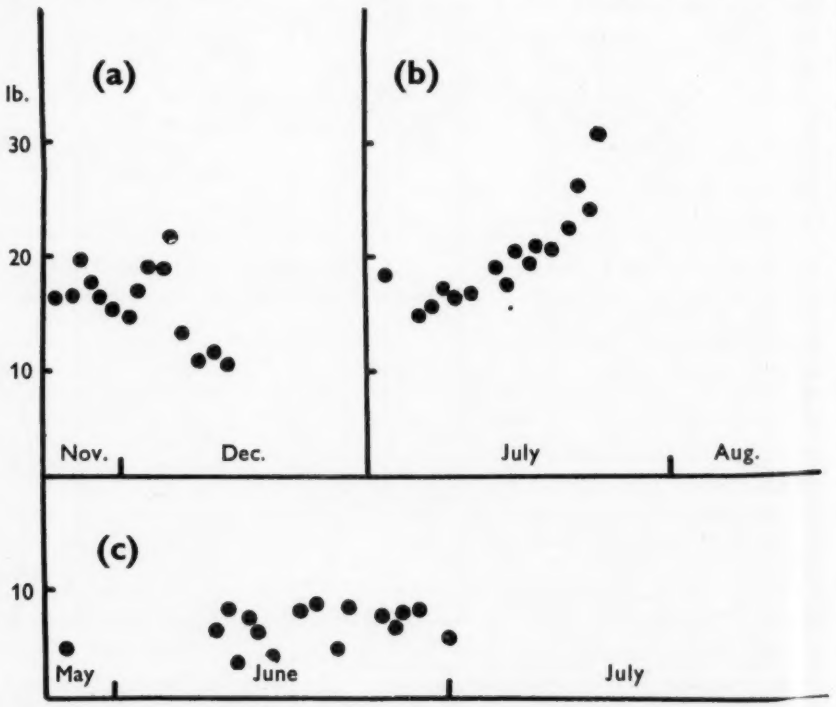

FIG. 7.—The effect of training on three muscles of patients with demyelinating disease. (*a*) Left biceps of Case 17. (*b*) Right triceps of Case 14. (*c*) Right biceps of Case 16.

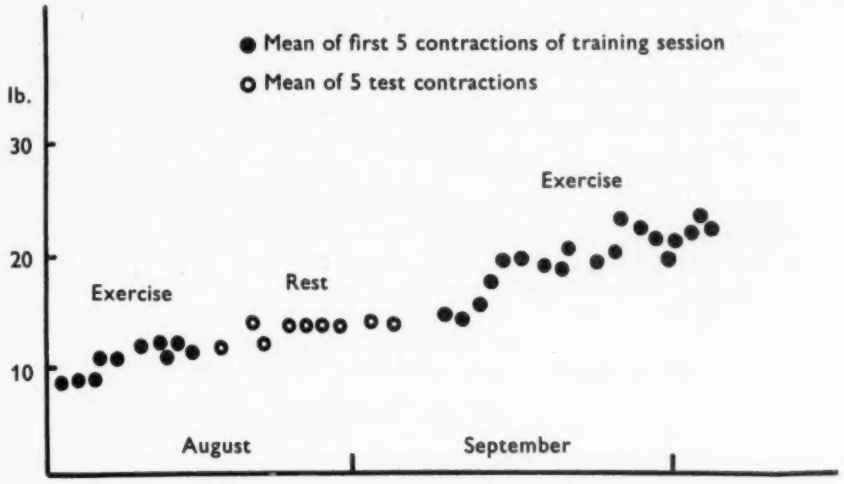

FIG. 8.—Effect of training on right biceps of Case 22 (cervical disc protrusion).

were the disease was fairly static. Case 18 showed no increase in strength with 12 sessions of exercise. Cases 15, 16, 17, and 19 showed a marked variability in strength both from day to day and between the individual contractions of the training sessions (Fig. 7). This made it difficult to discern a consistent trend. Thus Cases 15 and 16 showed a striking apparent improvement but in neither case was the difference between the means or the variance ratio for the regression significant. Case 17 showed an apparent deterioration which was significant, but, as Fig 7a indicates, it was not part of a steady trend, and it was not matched by her general condition which was improving.

Only with Cases 15, 18, and 21 was the diagnosis of disseminated sclerosis in any doubt. The alternative with Case 15 was basilar insufficiency and with Case 18 cervical spondylosis. Case 21 had a demyelinating illness but certain features in his case suggested Devic's disease rather than disseminated sclerosis.

Case 15 (*MN 125*).—A woman, aged 61, found the isometric exercises, of which she carried out 20 sessions, unusually fatiguing. This may account in part for her day-to-day variation in strength for she always did badly when she was tired. It was not evident that fatigue produced permanent ill effects but it would prevent her carrying out the next exercise session adequately.

Case 18 (*MN 1722*).—A man, aged 60, had weakness of the right arm and both lower limbs. He was admitted twice to the Neurological Unit, each time after a period of rest in bed after a respiratory infection which had been followed by increased stiffness of the lower limbs.

On his first admission 12 sessions of isometric exercise with the right triceps resulted in no increase in strength. Six months later the strength of the right biceps and triceps was found to have improved spontaneously although the lower limbs had grown weaker. He was given a course of weight-lifting exercises for the right biceps in which he carried out sessions on 16 days which produced stiffness of the arm muscles and marked generalized fatigue. Repeated measurements of the biceps and triceps muscles showed no change and his general condition improved.

Case 21 (*MN 3254*).—A man, aged 31, was improving after an episode of weakness in the limbs, ataxia, and retrobulbar neuritis eight months previously. When first seen he had some weakness of the right arm muscles. He carried out nine weight-lifting sessions with the right biceps during two weeks which were made progressively more strenuous, and isometric strength measurements were made. His arm became stronger and the exercises were abandoned when it was found that an hour of heavy weight lifting no longer produced marked fatigue.

The cases in this group which showed a significant increase in strength with exercise were passing into a stage of remission. Case 18 showed a deterioration with rest in bed which was partly reversed with exercise. It was not possible to demonstrate adverse effects from deliberately produced fatigue.

Miscellaneous Conditions.—The eight cases included in this group are summarized in Table I. Each patient, with the exception of Case 29, showed a significant increase in power in the muscle exercised and in each case this was materially useful to the subject. The treatment of Case 29 (MN 3128), who had a pseudo bulbar palsy and tetraparesis of gradual onset and probably a vascular pathology, coincided with a general deterioration in the patient's condition.

The patients with cervical spondylosis had unilateral weakness so it was not possible to compare one side with the other. In addition to exercise they were treated with neck traction and immobilization of the neck in a collar. Case 22 (MN 1736), however, had two courses of isometric exercise for the right triceps which were separated by a rest period lasting 25 days. His strength increased more rapidly when he was having exercise than during the period of rest (Fig. 8). Case 23 (MN 1567) had more than 75 exercise sessions for the left triceps and strength improved by 64%. Case 24 (MN 2001) registered

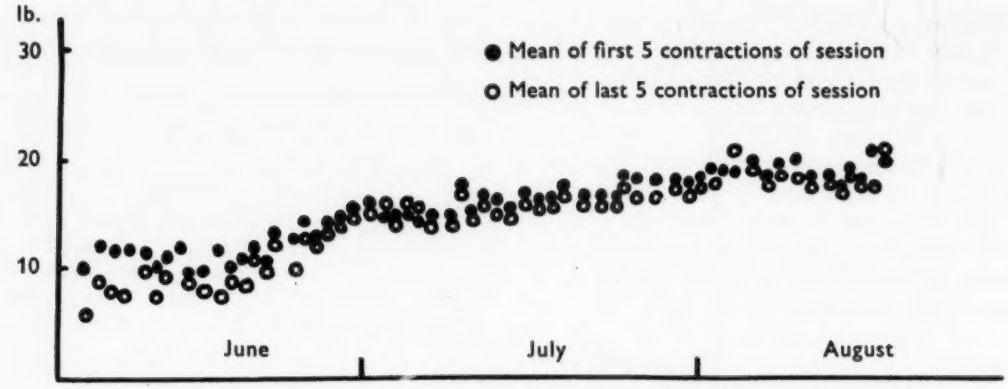

FIG. 9.—Effect of training on left triceps of Case 23 (cervical spondylosis).

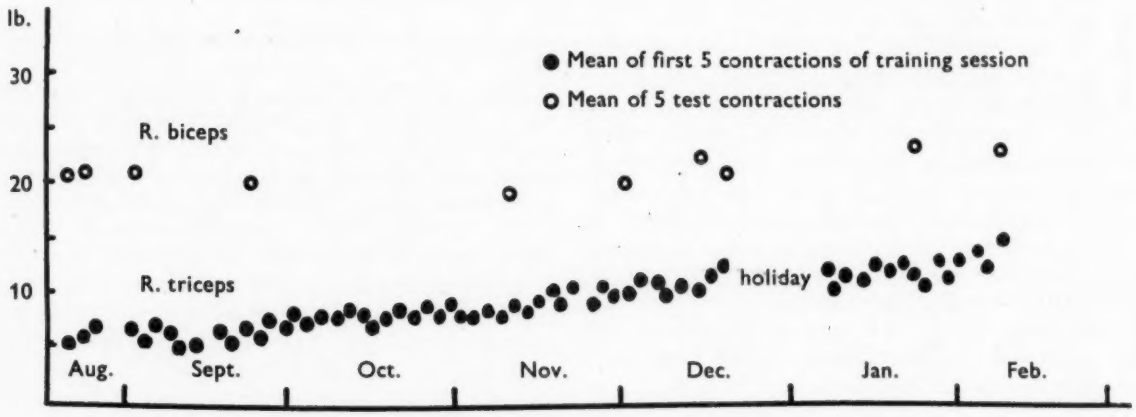

FIG. 10.—Effect of training on right triceps of Case 26 (poliomyelitis).

an improvement of 46% during 11 sessions of exercise with the right triceps. With Case 23 there was no improvement in maximum voluntary tension until after 12 sessions of exercise but before that there was a fall in the percentage decrement per session (Fig. 9). After 50 sessions strength was not further increased but he learned to increase his thrust against the dynamometer by a trick movement using his shoulder (Fig. 2). A subsequent intensive course of exercise using sessions of 60 contractions at 30-sec. intervals instead of 30 at one-minute intervals produced no further change.

Case 25 (*MN 2699*).—A man, aged 45, had enough radiological evidence of cervical spondylosis to account for pain in the shoulder, weakness of the left upper arm, and sensory symptoms in the lower limbs, but he also had wasting of both first dorsal interossei and widespread fasciculation which suggested that he might be developing motor neurone disease. However, with neck traction and 11 sessions of exercise for his left biceps the strength returned nearly to normal and nine months later this improvement was still maintained.

Case 26 (*MN 1340*).—A woman, aged 25, had had poliomyelitis eight months before. During 62 sessions of isometric exercise for the right triceps the strength of the muscle increased by 110%. During a pause of 19 days in this treatment the power of the arm did not change (Fig. 10). The other upper arm muscles were not exercised and improved more slowly. The increase in strength of the triceps continued till she ceased to exercise it. After that there was a slight falling off but it remained at about double its initial strength and nine months later no further change had taken place.

Case 27 (*MN 2369*).—A man, aged 41, developed a flaccid paresis of the arms with pain in the shoulders and C.5 sensory loss following a respiratory infection. He was treated with prednisolone and physiotherapy and his strength improved steadily over several months. After finishing his course of prednisolone he carried out eight sessions of isometric exercise with the left biceps, which appeared to improve more rapidly during the course of exercise than in the period preceding it, although his skill in developing trick movements made him difficult to assess.

Two weeks after admission to hospital he missed two

days of physiotherapy and an increase in the pain and stiffness of the arms was recorded.

Case 28 (MN 2339).—A man, aged 58, had a spastic right hemiparesis as the result of a cerebral thrombosis one year before. Nine sessions of isometric exercise for the right biceps resulted in an increase in strength of 47%. His spasticity, as measured by the ease with which clonus was elicited, became more pronounced.

Seven of the eight patients in this group had a condition in which recovery was taking place. In each of these seven cases the muscle which was exercised became stronger.

Discussion

Although other aspects of motor function, such as coordination, muscle tone, and endurance, are important, the experimental side of this study has been confined to the effects of exercise on the strength of a voluntary contraction. Other effects are less easy to measure and consideration of them has been based on clinical observations.

The physiological changes which exercise produces in nerve and muscle require to be understood if therapy is to be on a sound basis. Unfortunately little is known about them so that the aim here has been to establish a few of the facts on an empirical basis, in so far as this can be done with a small number of patients. Attention has been directed to three questions, namely, the effect on weak muscles of a system of exercise which has been shown to strengthen healthy muscle, the effect of deliberately produced fatigue, and the effect of confinement to bed without exercise.

It is accepted that systematic exercise will increase the strength of healthy muscle, but there is no agreement as to how this comes about and the most efficient way of developing a muscle by exercise is not known. Both isotonic and isometric exercises are effective, and Darcus and Salter (1955) have shown that if programmes of the same intensity are used the results are comparable. De Lorme (1945) has developed a technique of progressive resistance exercise based on experience gained by professional strength athletes. It consists of weight-lifting exercises which are made progressively more strenuous. There are many modifications of the technique but in each the subject lifts the maximum weight of which he is capable a fixed number of times each session. Hettinger and Müller (1953) and Müller and Hettinger (1953) suggest that a less strenuous programme is adequate. They state that a single isometric contraction each day will produce an increase in strength and a contraction of two-thirds maximum tension is adequate to produce the maximum possible training effect.

An increase in the strength of a muscle is associated with structural changes. A period of intense exercise produces transient swelling and a prolonged period of training leads to hypertrophy. There is no clear correlation, however, between the degree of hypertrophy and the increase in strength, and MacQueen (1954) differentiates between exercise programmes designed to produce primarily an increase in power and those leading principally to hypertrophy. A neuromuscular adaptation leading to more efficient use of the available motor units may be as important as a structural change in the individual fibres. This is supported by the early observation of Scripture, Smith, and Brown (1894) of cross-education which has been frequently repeated by other workers (Hellebrandt, Parrish, and Houtz, 1947; Darcus and Salter, 1955). If a muscle is exercised the contralateral muscle also becomes stronger.

Recently the effects of exercise on muscles weakened through injury or disease have attracted attention. De Lorme and Watkins (1948) have applied the technique of progressive resistance exercise to the treatment of disuse atrophy resulting from bone and joint disorders. Quantitative studies on the effect of exercise on muscle recovery in poliomyelitis were reported as early as 1916 by Lovett and Martin but opinion is still not unanimous as to its value. De Lorme and Watkins (1948) maintain that resistance exercise carried out over a period of years is valuable in that it develops those muscle fibres which retain their nerve supply and this is supported by the observations of Mead (1950) and Darcus (1955). On the other hand, Sharrard (1955) in a detailed study of the natural history of the disease, while he concedes that exercise may increase the rate of recovery, is doubtful whether it affects the ultimate level of recovery.

Russell (1947) and Horstmann (1950) have shown that exercise during the preparalytic phase of poliomyelitis increases the risk of paralysis supervening in the exercised muscles. This observation indicates that fatigue, apart from its local effects on the muscles, may affect the cells of the central nervous system. The effect of fatigue on muscle recovery in the later stages of poliomyelitis has been studied by Russell and Fischer-Williams (1954). They found that deliberately produced fatigue has no adverse effects on muscle recovery in this disease.

In other neurological conditions quantitative information is scanty. After cerebrovascular accidents active exercises are used increasingly in the treatment of paretic muscles and the clinical impression is probably justified that they hasten the recovery of strength as well as prevent contractures. In disseminated sclerosis exercises are often prescribed to strengthen weak muscles, improve coordination, and lessen spasticity, but the variable

natural course of the disease has made it difficult to assess their value, and McAlpine, Compston, and Lumsden (1955) have stressed the dangers of fatigue. Walton and Nattrass (1954), in their review of the muscular dystrophies, report adverse effects from rest in bed but suggest that fatigue may also be harmful.

In this study training has been mainly with isometric exercises. These are probably as effective as isotonic exercises (Darcus and Salter, 1955) and since they produce little fatigue it has been possible to study the effects of fatigue separately with a series of weight-lifting experiments. Isometric tension was chosen advisedly as the measurement of strength. Isotonic measurements are unsatisfactory as the maximum weight a subject can move can only be determined after several attempts so that when the final test is made the muscle is fatigued. In making the strength measurements, positioning of the patient was found to be critical so that all measurements were made by the same observer. The consistent linearity of the curves relating tension to the integrated electromyogram, which conforms to the earlier observations of Lippold (1952), has been taken as indicating the infrequency of trick movements when care is taken. The fact that the same curve is reproducible in the same subject on different occasions suggests that the dynamometer measurements are reasonably reliable.

Effect of Isometric Exercise.—The effects of isometric exercise on healthy subjects were consistent in that all the subjects showed a substantial increase in strength. The exercises did not produce fatigue so it is evident that a muscle can be made stronger without fatiguing it.

Of the cases with a primary muscular disorder, only Case 1 showed an improvement which could not be partly explained by spontaneous recovery or the effects of other treatment. The improvement was slow but it is significant that a training effect is possible at all with dystrophic muscle. It cannot be said how far the patients with polymyositis would have improved if exercise had not been given. Changes in the contralateral muscles may have been due to cross-education (Scripture *et al.*, 1894). The only occasions, however, where the changes associated with exercise were striking were during improvement after a relapse. Here the correction of disuse atrophy was an important factor, and it is probably true that the main indication at present for exercise in muscular disorders is in the treatment and prevention of wasting due to disuse.

In the group which includes six patients with motor neurone disease the improvement in four of the 12 muscles exercised could not have been the result of spontaneous recovery as in each case the disease was progressing. Of the four muscles three were triceps which is a muscle used to a limited extent in everyday life. The fourth muscle was the biceps of an arm so weak that it had fallen largely into disuse. Müller and Hettinger (1953) have shown that if the limb of a healthy subject is immobilized in plaster its response to training after disuse atrophy has developed is three times as rapid as a training effect observed in the same muscles before immobilization. None of these muscles showed so rapid an improvement but with Case 7 (Fig. 6a) the improvement during the first nine sessions was more rapid than with any of the normal subjects. The two triceps muscles of Case 8 showed no change during the first eight sessions and then a striking and rapid change took place. With the biceps of Case 9, although no change was noted in the first five contractions of a training session until several weeks had passed, toward the end of her fifth exercise session she was working up to a contraction nearly as great as the maximum she attained later. Her exercise sessions were comparatively infrequent and it is possible that in each session she had to work off the effects of disuse in the intervening period. Thus in this group the sole effect of exercise may have been the correction of wasting due to disuse.

Of the seven patients with demyelinating disease who received isometric exercises, only Cases 14 and 20 showed improvement in the muscle exercised. This was more rapid than is usual for a training effect and occurred when the disease was entering a remission. The variability in strength which these patients showed from day to day and from contraction to contraction is in keeping with the known character of the disease.

The remaining cases with one exception all improved with exercise. They were patients in whom the disease had a natural tendency to recover but in some it appears that exercise increased the rate of recovery. Case 26 had reached a stage where the natural rate of recovery is slow. The exercised muscle improved at a rate faster than the other affected muscles and during a pause in her treatment progress stopped until she started to exercise again. After she had finally ceased to exercise no further improvement occurred. This result in a case of poliomyelitis is in keeping with the experience of De Lorme and Watkins (1948) and Darcus (1955). Case 22 likewise improved more rapidly during two periods of exercise than during the intervening rest period. Case 28 improved during treatment more rapidly than during the previous year since his original vascular accident. Case 23 did not start to become stronger till 12 days after he had started

to exercise, and although one can ascribe his improvement to neck traction and a cervical collar it is possible that these merely alleviated the root irritation and allowed the muscle to respond to exercise. It is of interest that with this patient after a certain stage no amount of additional exercise would produce any further change, indicating that the ultimate level of recovery is determined by the amount of structural damage that has taken place.

The Effects of Fatigue.—Although fatigue may contribute to the adaptation of a muscle to exercise the isometric experiments indicate that it is not an essential factor in increasing strength. There remains the question whether it may delay muscle recovery. If it increases the risk of paralysis developing in preparalytic poliomyelitis (Russell, 1947) it may also cause deterioration in other conditions where anterior horn cells are degenerating, such as motor neurone disease. McAlpine *et al.* (1955) have described patients with disseminated sclerosis whose symptoms first appeared after severe exertion, paralysis developing in the muscles exercised. Patients with muscular dystrophy often ask whether fatigue will do their muscles any harm and it is important to be able to give them appropriate advice.

Although the isometric exercises did not fatigue the healthy subjects a number of the patients with weak muscles complained of aching in the muscles during a session and found that they could not exert as much force at the end of a session as at the start. An improvement in the maximum tension exerted at the beginning of a session was often preceded by a decrease in the decrement of strength during the sessions (Fig. 9) indicating that these exercises had an effect on endurance as well as on strength. Of the seven patients who carried out isotonic exercises which caused considerable fatigue, none showed an increase in strength greater than that resulting from isometric exercises.

The weight-lifting exercises were designed to produce fatigue. In no case did these exercises affect the rate of deterioration or result in deterioration where none was occurring. Of this group of cases two had dystrophic muscle (Cases 1 and 6), two had motor neurone disease (Cases 7 and 13), two had demyelinating disease (Cases 18 and 21), and one had syringomyelia (Case 9).

A further case of motor neurone disease (Case 8) found the isometric exercises to the triceps muscles particularly fatiguing and the sessions were followed by increased fasciculation. The muscles, however, became stronger so that the fasciculation does not necessarily indicate an increase in the rate of anterior horn cell destruction. All six cases of motor neurone disease were right handed but only three showed the disease to be more advanced on the right side of the body.

Two cases with demyelinating disease were deliberately exercised to exhaustion without ill effects. A further two found the isometric exercises fatiguing, but did not suffer any permanent harm. They found that when they became tired they were unable to carry out their exercises adequately.

The amount of exertion carried out by these patients was small compared with that undergone by those who have been described as developing muscular weakness through poliomyelitis or disseminated sclerosis after severe exercise such as climbing or cross country running when they were still fit. Nevertheless the weight-lifting exercises were adequate to fatigue appreciably patients weakened through prolonged illness. They were more fatiguing than any likely to be carried out in the course of treatment.

The number of cases of muscular dystrophy is small, and although it has not been possible to demonstrate any deleterious effects from exercise, it is possible that certain patients, particularly those where the disease is more rapidly progressive, may harm muscles through excessive use.

The Effects of Rest.—Rest was not deliberately prescribed for experimental purposes but certain patients had periods of rest in bed enforced through circumstances or intercurrent disease.

Case 3, who had polymyositis, had three relapses following infections and it is likely that the infection itself was an important disturbing factor. Nevertheless she always noticed that any period of rest in bed, as after a cold, would lead to increased weakness which it would take several days of active use of the muscles to relieve. Muscle weakness, which at the time was associated with stiffness, was most severe during the period of prolonged rest in bed when she was in the respirator.

Case 8, who had motor neurone disease, noticed an increase in spasticity if he was confined to bed and disuse aggravated his weakness.

Disseminated sclerosis often relapses after intercurrent infections which appear to reactivate the disease. Case 20 had a severe relapse which necessitated admission to hospital after an attack of influenza. Case 18, on the other hand, was twice admitted to hospital after an intercurrent infection, not because the disease was more active but because rest in bed had led to an increase in muscular stiffness which was subsequently relieved by exercise.

Conclusion

The place of exercise in the management of neurological disease is an important but a restricted

one. As a means of increasing the strength of muscles paralysed by degenerative disease it is probably without value. But these patients may develop weakness of relatively unaffected muscles due to disuse, particularly if they are confined to bed for any reason and this weakness is relieved by exercise. Likewise the affected muscles, if they are spastic, will show an increase in stiffness if they are rested. It is worthwhile to give active exercises to patients who are recovering from a paralytic lesion as these may increase the rate of recovery. They need not cause fatigue to be effective, but any fatigue which they incidentally produce is unlikely to do harm.

Summary

Isometric exercises are an effective means of improving the strength of healthy individuals. They need not cause fatigue to be effective.

It is possible to increase the strength of a patient with a muscular dystrophy, but very slowly, and progress of the disease may undo any benefit achieved.

Weakness resulting from degenerative disease of the nervous system is not affected by exercise, unless the loss of strength is the result of disuse.

When a paralysed muscle is recovering either through specific treatment, or spontaneously, there is evidence that active exercise increases the rate of recovery.

Patients with motor weakness due either to primary muscular disease or to disease of the central nervous system may deteriorate with rest in bed. This is due in part to disuse, in part to an increase in stiffness. Both these effects may be corrected by active exercise.

No adverse effects have been shown to result from fatigue in primary muscular or neurogenic paresis.

I wish to thank the physicians in the Neurological Unit at the Northern General Hospital, Edinburgh, for permission to study their cases.

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References

Bates, J. A. V., and Cooper, J. D. (1954). *J. Physiol.* (*Lond.*), 123, 28P.

Darcus, H. D. (1955). *Poliomyelitis:* Papers and Discussions presented at the Third International Poliomyelitis Conference [Rome, 1954], p. 446. J. B. Lippincott, Philadelphia.

—— (1956). Personal communication.

—— and Salter, N. (1955). *J. Physiol.* (*Lond.*), **129**, 325.

De Lorme, T. L. (1945). *J. Bone Jt Surg.*, **27**, 645.

——and Watkins, A. L. (1948). *Arch. phys. Med.*, **29**, 263.

Edwards, R. G., and Lippold, O. C. J. (1956). *J. Physiol.* (*Lond.*), **132**, 677.

Hellebrandt, F. A., Parrish, A. M., and Houtz, S. J. (1947). *Arch. phys. med.*, **28**, 76.

Hettinger, T. and Müller, E. A. (1953). *Arbeitsphysiologie*, **15**, 111.

Horstmann, D. M. (1950). *J. Amer. med. Ass.*, **142**, 236.

Lippold, O. C. J. (1952). *J. Physiol.* (*Lond.*), **117**, 492.

Lovett, R. W., and Martin, E. G. (1916). *J. Amer. med. Ass.*, **66**, 729.

McAlpine, D., Compston, N. D., and Lumsden, C. E. (1955). *Multiple Sclerosis*, p. 39. E. and S. Livingstone, Edinburgh.

MacQueen, I. J. (1954). *Brit. med. J.*, **2**, 1193.

Mead, S. (1950). *J. Amer. med. Ass.*, **144**, 458.

Müller, E. A., and Hettinger, T. (1953). *Arbeitsphysiologie*, **15**, 223.

Russell, W. R. (1947). *Brit. med. J.*, **2**, 1023.

—— and Fischer-Williams, M. (1954). *Lancet*, **1**, 330.

Sharrard, W. J. W. (1955). *J. Bone Jt Surg.*, **37B**, 63.

Scripture, E. W., Smith, T. L., and Brown, E. M. (1894). *Stud. Yale psychol. Lab.*, **2**, 114.

Simpson, J. A., and Lenman, J. A. R. (1959). *Electroenceph. clin. Neurophysiol.*, **11**, 604.

Walton, J. N., and Nattrass, F. J. (1954). *Brain*, **77**, 169.

Neurol. Neurosurg. Psychiat., 1959, **22**, 195.

A CASE OF SPONTANEOUS DISSECTING ANEURYSM OF THE INTERNAL CAROTID ARTERY

BY

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Dissecting aneurysm of the internal carotid artery, without preceding trauma, is a rare event. We have been unable to find a previous case report.

One case of dissecting aneurysm of the internal carotid artery following head injury has been reported (Dratz and Woodhall, 1947), and two cases after carotid puncture for arteriography (Sirois, Lapointe, and Côté, 1954; de Grood, 1954) where the common carotid dissection extended into the internal carotid arteries. As an extension of a dissecting aneurysm of the aorta Shennan (1934) reported five cases.

The following case, apart from its rarity, is of both radiological and pathological interest.

Case Report

A.R. (N.H. 75263), a man, 41 years of age, was admitted to the National Hospital, Queen Square, on October 16, 1957, under the care of Dr. John Marshall.

The history obtained on admission was from an accompanying letter which stated that the patient had developed a right hemiparesis on the day before admission. The development of paresis was over a period of several hours. There was a past history of cystitis.

At the time of admission he was conscious but unable to speak or comprehend spoken commands. His eyes were deviated to the left and he appeared to have a right homonymous hemianopia. There was a right hemiparesis with weakness of the right side of the face. The lower limb was weaker than the upper limb. Tone was increased in both upper limbs and in the right lower limb. The tendon reflexes were more active on the right. A grasp reflex was present on the left side and the plantar responses were bilaterally extensor. There was a response to pin prick on both sides. The blood pressure was 149/95 mm. Hg. No other abnormality was found on general examination.

Lumbar puncture soon after admission produced clear cerebrospinal fluid at a pressure of 160 mm. of C.S.F., and it contained three lymphocytes per c.mm., 25 mg. of protein per 100 ml., and the C.S.F. Wassermann reaction was negative. The erythrocyte sedimentation rate was 51 mm. in one hour and 56 mm. in two hours.

The day after admission carotid arteriography was carried out. The left common carotid artery was punctured below the level of the fourth cervical vertebra, and two injections, 8 ml. each, of 45% "hypaque" were made. The radiographs showed contrast medium in a normal-looking common carotid artery for the upper 4 cm. of its course, and a normal-looking external carotid artery. In the internal carotid artery, however, about 1·5 cm. from its origin there was a localized filling defect extending for approximately 5 mm. Three centimetres above its origin the lumen tapered to a very narrow channel which reached its maximum degree of constriction at a point 4·5 cm. from the origin of the artery. Approximately 6 cm. from the origin of the artery the shadow of the contrast medium widened again and was seen to outline the intracranial course of the artery and its branches (Figs. 1a, b, and c), but inadequately. In order to outline the entire length of the left common carotid artery, the artery was punctured again as low down in the neck as possible, and two injections, 8 ml. each, of 45% "hypaque" were given. This demonstrated the lower part of the common carotid artery, which appeared normal, and the deformity of the internal carotid artery was again demonstrated. It was considered that the left internal carotid artery was partially occluded by atheroma and thrombus.

Anticoagulant therapy was begun but the patient became progressively more drowsy and three days after admission he developed a left third cranial nerve palsy. The left lateral ventricle was tapped through a burr hole. This showed cerebrospinal fluid under normal pressure. The patient died later the same day, October 19, 1957, four days after the onset of his illness.

Necropsy

Necropsy was carried out 43 hours after death and the principal findings were as follows:

General Examination.—The body was that of a well nourished, middle-aged male with no skin lesions other than those due to the surgical procedures. There were dense adhesions at the apex of the right lung. Subapical caseous nodules were present in the upper lobes of both lungs. The heart weighed 420 g.; the myocardium, endocardium, and valves were normal. There was mild patchy atheroma of the coronary arteries and of the aorta. The liver

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weighed 1,950 g., its cut surface pale and yellowish. The spleen weighed 200 g. and the Malpighian corpuscles were more prominent than usual. The left kidney weighed 300 g. and was about twice the size of the right kidney. On section the left kidney showed a normal architecture. The parenchyma of the right kidney was almost wholly replaced by circumscribed areas of caseous material. The wall of the right ureter was thickened and its lumen contained caseous material. The bladder wall was thickened and its mucosa inflamed. The seminal vesicles were enlarged, but the testes appeared to be normal.

Histological Examination.—The caseous nodules in the lungs, kidney, ureter, and seminal vesicles were tuberculous in appearance. Numerous tubercle bacilli were demonstrated in the renal lesions. Microscopically the prostate also contained caseous nodules. Gross fatty change was present in the liver. No amyloid change was demonstrated in the liver, spleen, or kidneys.

Brain.—The left hemisphere was enlarged and pale. It was softened over its anterior two-thirds. Temporal herniation was present on the left side. Coronal sections through the cerebrum showed softening of the left frontal and parietal lobes, including the cortex, white matter, and the basal ganglia in the distribution of the left anterior and middle cerebral arteries. In places there were petechial haemorrhages in the softened cortex. There was also some softening of the medial part of the right frontal lobe in the distribution of the right anterior cerebral artery. The lateral and third ventricles were displaced to the right side. The cranial part of the brain-stem was displaced caudally and scattered haemorrhages were present in the cranial part of the brain-stem. The circle of Willis was complete. The right anterior cerebral artery was narrow from its origin to the anterior communicating artery, and beyond this point it contained ante-mortem blood clot filling the lumen and adherent to the wall. The right posterior cerebral artery arose principally from the right

(*a*) (*b*) (*c*)

FIG. 1.—Left common carotid arteriogram.

(*a*) The needle point, which is not shown, must be proximal to the end of the common carotid artery. The external carotid artery and its branches are outlined. The internal carotid artery tapers 3 cm. above its origin.

(*b*) Film taken 1·5 seconds after film (*a*). Contrast medium still persists in the internal carotid artery but beyond the constriction the artery widens and contrast medium is present in the carotid siphon and its branches.

(*c*) Film taken three seconds after film in Fig. (*a*). Contrast medium still persists in the internal carotid artery.

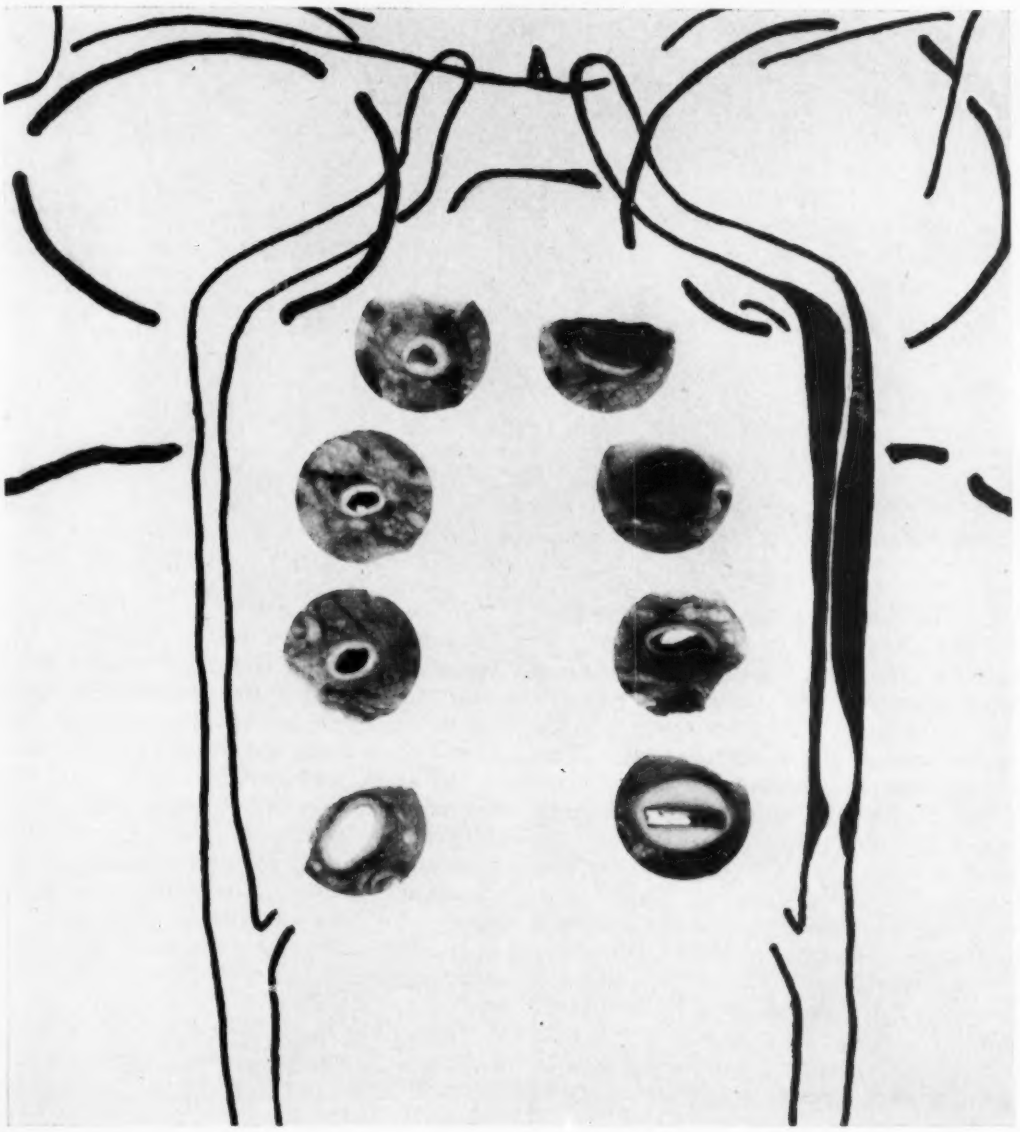


FIG. 2.—A combined diagram and photograph showing a reconstruction of the internal carotid arteries after cutting them into transverse sections. Some of these sections are shown opposite the appropriate portion of the artery (for description see text). Sections shown in Figs. 3, 4, 5, and 6 were taken from the sites indicated.

internal carotid artery, and only a narrow vessel connected it with the basilar artery. The walls of the major arteries appeared healthy.

Histological Examination of the Brain.—Softened areas from the right and left frontal lobes showed the changes usually seen in recent infarction. The neurones were shrunken. Polymorphonuclear cells and mononuclear cells were present in the parenchyma, particularly around the blood vessels and in the leptomeninges. Astrocytes appeared to be increased in number and there was endothelial hyperplasia of the blood vessels. Myelin in the softened areas stained poorly. The lesions in both frontal lobes appeared to be of approximately the same age.

Arteries of the Neck.—The carotid and vertebral arteries and arch of the aorta were removed en bloc with the cervical spine and base of the skull. After one week of fixation in formol saline the arch of the aorta, carotid arteries to the base of the skull, and vertebral arteries as far as their entry into the vertebral transverse processes were removed for

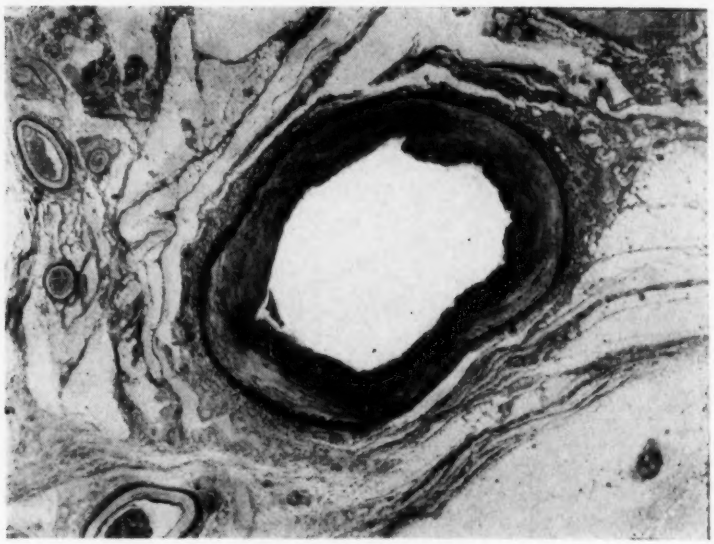


FIG. 3.—Transverse section through the right internal carotid artery showing the irregularity and deficiency of the elastica in the media. This section was taken a little above the level of the section from the left side (Fig. 4). The levels are indicated in Fig. 2. Weigert's elastic stain (× 12).

sectioning. The remaining bony parts were then decalcified in 5% nitric acid.

Horizontal sections were cut through the carotid and vertebral arteries.

The arch of the aorta, innominate artery, and the right common carotid artery were normal. There were two angiographic puncture wounds in the anterior wall of the left common carotid artery, and a moderate amount of blood staining of the surrounding muscle. This artery was otherwise normal.

The vertebral arteries were normal throughout their entire length. The right internal carotid artery was a little narrower than the left at its origin (right 7 mm. diameter, left 8 mm. diameter). Two centimetres above its origin it narrowed to 4 mm. diameter and remained narrow as far as the base of the skull (Fig. 2) after which for the rest of its course it was normal.

One centimetre above its origin the lumen of the left internal carotid artery was diminished by opposing plaques of atheroma. This narrowing persisted for 5 mm. and then the lumen returned to its previous diameter. At 3 cm. above its origin the lumen of the artery was almost completely occluded by haemorrhage within its wall. For a short distance this dissecting haemorrhage was confined to the anterior wall of the artery, and above this it surrounded the whole lumen of the vessel. The intramural haemorrhage extended for between 3 and 4 cm. to the point where the artery turned antero-medially beneath the floor of the middle fossa. Here there was an intimal tear. Beyond this point the artery appeared normal (Fig. 2).

Histological Examination of Arteries.—After embedding in paraffin and/or celloidin, transverse sections were cut through the arteries and stained with haematoxylin-eosin, haematoxylin-van Gieson, thionine blue, Weigert's elastic tissue stain, Verhoeff's elastic tissue stain, and Masson's trichrome.

The aortic wall showed a little cystic change in the media but was otherwise normal.

In the media of the left and right common carotid arteries there was a moderate increase of metachromatic material. The elastic tissue and muscle appeared normal. Atheroma was present.

The left external carotid artery also showed an increased amount of metachromatic material in the media.

The wall of the right internal carotid artery contained an increased amount of metachromatic material in its media and cystic change was well marked. The elastic tissue pattern was abnormal; there was less elastic tissue than usual, and the fibres appeared to be shorter and thicker than normal (Fig. 3). The muscle of the media appeared to be comparatively normal. Vascularization of the media was not evident.

The left internal carotid artery (Fig. 4) showed similar changes to those of the artery on the right, but in addition there was haemorrhage into the wall of the artery in the outer part of the media (Fig. 5). A longitudinal section through the artery at the lower end of this intramural haemorrhage showed a tear through the media and intima into the lumen of the vessel (Fig. 6). Thus there were intimal tears at both ends of the dissecting haemorrhage. The upper tear was mentioned previously in the

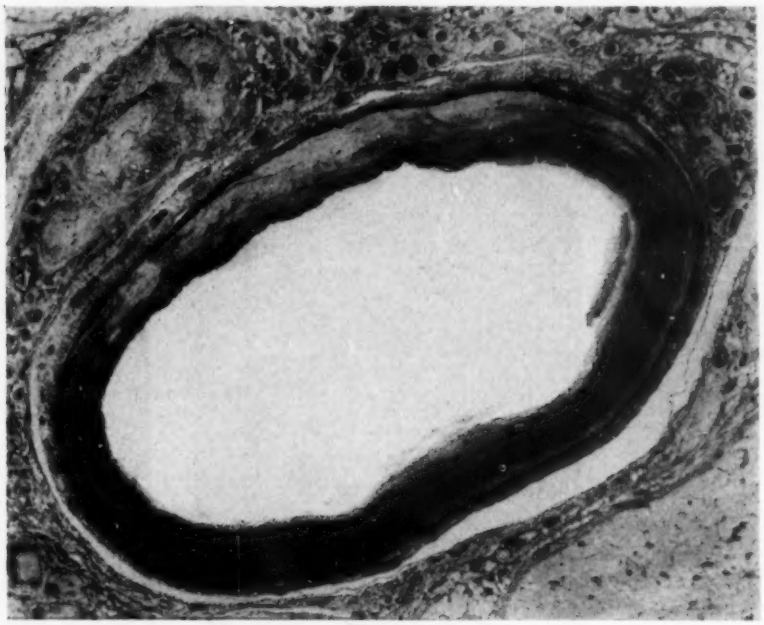
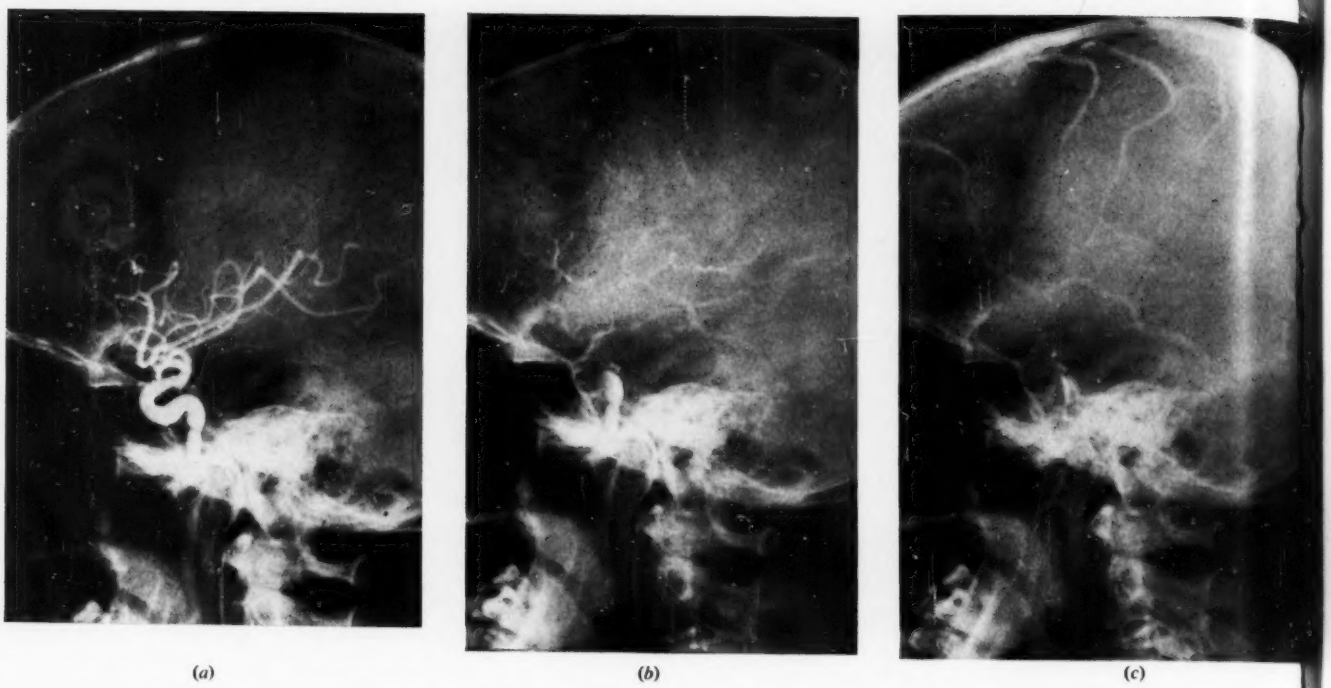


FIG. 4.—Transverse section through the left internal carotid artery just below the site of the dissecting haemorrhage in its wall. The posterior part of the wall in the upper part of the photomicrograph appears to be normal, but in the anterior wall the elastica of the media is deficient. Weigert's elastic stain (× 12).

FIG. 5.—Transverse section of the left internal carotid artery a little above the lower end of the dissecting haemorrhage. Blood clot has fallen out of the media in preparing the section; however, the position of the blood clot is shown to be in the outer part of the media. The deficiency in the elastica of the media is well shown. Weigert's elastic stain (× 30).

FIG. 6.—Longitudinal section through the lower end of the dissecting aneurysm to show the intimal tear. Weigert's elastic stain (× 27).



(*a*) (*b*) (*c*)

FIG. 7.—Internal carotid arteriogram performed on another patient showing appearances produced by accidental intramural injection.

(*a*) Note the tip of the catheter rendered opaque by contrast medium. There is filling of the internal carotid artery and its branches.

(*b*) Film taken two seconds after (*a*). The contrast medium has left the major branches of the internal carotid artery, but some still persists in the internal carotid artery in the neck and its siphon.

(*c*) Film taken four seconds after (*a*). The ma portion of the contrast medium has already reach the cerebral veins. A narrow streak still persists in t line of the wall of the internal carotid artery in the ne and in its siphon.

macroscopic description but was not examined microscopically as this part of the artery had been in decalcifying fluid.

Discussion

Radiology.—The radiological appearances seen in this case indicate the presence of a dissecting aneurysm of the internal carotid artery. There is some similarity to those seen in thrombosis of the artery and to those seen where atheromatous plaques are present, but in the former condition no contrast medium passes the site of thrombosis and in the latter small, localized filling defects are present in the shadow of contrast medium filling the arterial lumen.

In carotid angiography the contrast medium may occasionally be injected into an artery when the needle point has accidentally penetrated the arterial wall. This, however, gives a characteristic picture. Fig. 7 illustrates the appearances in such a case. The serial films show that the main part of the contrast medium has passed into the cerebral circulation, while a small part has passed along the wall of the vessel, stripping the tissues in its path and producing a double shadow, the translucent area between representing the arterial wall. In such cases the shadow of contrast medium disappears in less than 10 minutes.

Cases of intramural injection of contrast medium have previously been described by Sirois, Lapoint, and Côté (1954) and by de Grood (1954).

Pathology.—Gore (1952, 1953) noted two main types of medial degeneration in cases of dissecting aneurysm in the aorta. These were (1) the elastic tissue type, more often seen in people under the age of 40, in which the elastica was severely damaged, with relative sparing of the muscle fibres, and in which there was an accumulation of basophilic ground substance; and (2) the muscle tissue type where the muscle was severely damaged, with only slight changes in the elastica. Vascularization of the media was a prominent feature in both groups. In our case there was severe damage to the elastica and there was an accumulation of metachromatic material (basophilic ground substance) in the media. In these respects it conforms with the elastic tissue type of medial degeneration.

Vascularization of the media was not present.

This, and the recent tears in the intima, are evidence that, in this case, the blood in the media came direct from the lumen of the artery and could not have come from any abnormal vascularization of the media. Such a source of haemorrhage has been suggested in other cases of intramural haemorrhage.

The constant finding of medial degeneration in cases of dissecting aneurysm is considered by some authors to be an important factor in association with the development of the condition. It is often difficult to decide whether this medial degeneration antedates or follows the development of the aneurysm. In our case the presence of similar changes in the otherwise healthy carotid artery is evidence that the medial degeneration preceded the aneurysm.

The presence of an increased amount of metachromatic material in the media is thought to be an important early feature of the elastic tissue type of degeneration in man, and it is found constantly in experimental lathyrism in animals (Menzies and Mills, 1957), where dissecting aneurysms are a prominent feature. In this condition, due to an upset in enzyme metabolism, an accumulation of metachromatic material is found widespread throughout bones and the aorta (Menzies and Mills, 1957) and possibly in other tissues. Meyer and Rapport (1950, quoted by Menzies and Mills, 1957) consider this metachromatic material to be chondroitin sulphate. This substance is also found to be increased in association with amyloid deposits. Our patient had chronic caseating tuberculosis, which is often associated with secondary amyloidosis, and although amyloid deposits were not seen in the kidneys, liver, or spleen, it is always possible that the same process which can give rise to secondary amyloidosis may here have produced an excess of histologically similar abnormal material in the carotid arteries.

Summary

A case of spontaneous dissecting aneurysm of the internal carotid artery, in a male of 41 years, is presented.

The radiological and pathological findings are discussed.

We are indebted to Dr. John Marshall for permission to present this case, to Professor W. Blackwood and Dr. Hugh Davies for their advice and help, and to Mr. J. Mills and to the staff of the photographic department of the Institute of Neurology for the photographs.

References

Dratz, H. M., and Woodhall, B. (1947). *J. Neuropath.*, **6**, 286.
Gore, I. (1952). *A.M.A. Arch. Path.*, **53**, 142.
—— (1953). *Ibid.*, **55**, 1.
Grood, M. P. A. M. de (1954). *Rev. neurol.*, **90**, 661.
Menzies, D. W., and Mills, K. W. (1957). *J. Path. Bact.*, **73**, 223.
Shennan, T. (1934). Med. Res. Coun. Spec. Rep. Series, No. 193.
Sirois, J., Lapointe, H., and Côté, P. E. (1954). *J. Neurosurg.*, **11**, 112.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 202.

RUPTURED POSTERIOR FOSSA ANEURYSMS AND THEIR SURGICAL TREATMENT*

BY

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The use of vertebral angiography in the investigation of subarachnoid haemorrhage has enabled the presence of posterior fossa aneurysms to be detected during life. The clinical and radiological localization of aneurysms in this site is now of importance, for with modern neurosurgical techniques, including hypothermia, a number of these lesions are operable. Certain anatomical features which will be discussed later should render their surgical treatment in some ways easier than that of aneurysms in a supratentorial location.

Aneurysms in the posterior fossa are here defined as lying below the level of the tentorium and situated on the vertebral artery, the basilar artery, and their branches up to the basilar bifurcation. Aneurysms on the posterior cerebral artery and those presenting directly upwards from the termination of the basilar artery are not included, as they are truly aneurysms of the circle of Willis and have different symptoms and require an entirely different surgical approach compared with those situated below the tentorium.

Before the use of vertebral angiography, the diagnosis of posterior fossa aneurysm was usually made at necropsy after death due to subarachnoid haemorrhage, or occasionally on surgical exposure, when an aneurysm had presented as a space-occupying lesion in the posterior fossa. Some aneurysms were symptomless in life, and then were accidental findings in death due to other causes.

The figures of incidence may be obtained from published series of cases of subarachnoid haemorrhage. McDonald and Korb (1939) reviewed 1,023 cases of intracranial aneurysm from the literature including 786 examples of rupture, and of those 143 (18%) were on the basilar-vertebral trunks. Richardson and Hyland (1941) in a series of personal cases which contained 27 ruptured aneurysms, found that six, or 22%, were in the posterior fossa. Walton (1956) included eight (6·5%) among 122 ruptured aneurysms in the Newcastle series. The incidence shows a tendency to a reduction in recent series which has been ascribed to exclusion of aneurysms due to syphilitic and atheromatous changes. Walsh (1957) in a surgical series of cases of subarachnoid haemorrhage, found an incidence of 6% and attributed this lower figure to the fact that vertebral angiography was not carried out as a routine. An incidence of 15% on the basilar-vertebral circulation was accepted by Walton and Walsh, but if aneurysms of the posterior part of the circle of Willis were excluded, the figure would be about 10%.

Some information about the clinical aspects of subarachnoid haemorrhage due to posterior fossa aneurysms may be found in the literature. Dandy (1944) considered bilateral motor loss as evidence of haemorrhage from an aneurysm of the basilar or vertebral arteries. The late Sir Hugh Cairns (1952) discussed the disturbance of consciousness associated with disorders of the brain-stem. He quoted a case of subarachnoid bleeding into the posterior fossa due to a laterally situated aneurysm of the basilar artery, which produced homolateral pain in the head, followed by loss of consciousness with stertorous breathing and four convulsive attacks, with recovery. He considered that abrupt losses of consciousness, respiratory disturbances with hypersecretion of mucus, and weakness of the legs were characteristic of dysfunction of the lower brain-stem.

Focal cranial nerve signs mentioned by Walton (1956) in his review of cases from the literature and the Newcastle series, included nystagmus, external rectus and facial palsies, premonitory attacks of vertigo, and deafness. Pain in the trigeminal territory was a common feature of aneurysms on the internal carotid artery and its terminal branches, but ipsilateral headache was mentioned in one patient with a basilar aneurysm lying in the left cerebello-pontine angle. Contraction of the pupils, although a well recognized feature of pontine haemorrhage, was not stressed as a sign of aneurysms of the posterior fossa. Subarachnoid bleeding has

*Based on communications read at the Association of British Neurologists and the Society of British Neurological Surgeons, November, 1957.

been observed by Robertson (1949) to cause convulsions, plastic disorders of tone, and fluctuating hemiparesis. He found that fits of a tonic type might result if blood clot formed on the ventral surface of the brain-stem. Brain (1955) considered that quadriplegia and various forms of "crossed paralyses" might occur due to a leaking basilar aneurysm, and that the head retraction was likely to be conspicuous when haemorrhage resulted from an aneurysm in the posterior fossa.

Accounts of surgical treatment usually consist of reports of a single case. Dandy (1944) wrote of a large aneurysm on the vertebral artery which was shelled out easily but the patient died from the effect of high pressure in the posterior fossa. Six successful operations have been reported. Schwartz (1948) described the excision of an aneurysm on an aberrant artery related to the internal auditory artery. Rizzoli and Hayes (1953) recorded one case of a posterior inferior cerebellar aneurysm. The patient presented with bilateral sixth nerve palsies and multiple subhyaloid haemorrhages in the fundi. The location of the aneurysm in the posterior fossa was suspected by the presence of hydrocephalus on ventriculography with a shift of the fourth ventricle to the right. The sac was completely excised with its segment of artery and a reasonable neurological recovery eventually followed. Norlén and Barnum in the same year described symptomatic relief after treatment of one large vertebral aneurysm by a decompression and packing with muscle, and also the successful excision of an aneurysm on the posterior inferior cerebellar artery in a man aged 26 who was alive and well six years later.

Two cases of aneurysm of the posterior inferior cerebellar artery treated surgically have been described by DeSaussure, Hunter, and Robertson (1958). The first patient, in addition to severe occipital headache, had unusual focal symptoms at the onset consisting of weakness and tingling of the left extremities with blurred vision in the left homonymous half-fields, which suggested spasm extending to the right posterior cerebral artery and circle of Willis. The authors in both cases adopted the procedure of "trapping" the aneurysm between proximal and distal clips with occlusion of the posterior inferior cerebellar artery. They considered that the mild ataxia which resulted was preferable to the risk of further haemorrhage.

Uihlein and Hughes (1955) reported exploration of 14 aneurysms on the basilar-vertebral system. Eight of the 14 patients died of aneurysmal rupture, but no definitive treatment was undertaken for these lesions.

Although factual information about these aneurysms is increasing, the view that posterior fossa arterial lesions are probably untreatable, still tends to influence our attitude to further investigation and to dissuade us from performing vertebral angiography routinely after negative carotid arteriograms. Walton (1956), after reviewing a variety of papers dealing with the surgical treatment of aneurysms, made the following statement: "Although occasionally posteriorly situated aneurysms have been operated upon with success, the great majority of those on the basilar and many on the vertebral and cerebellar arteries are not at present operable". Walsh (1957) also commented that "few cases of posterior fossa aneurysms are at present amenable to surgical treatment".

Theoretical considerations, however, suggest that these aneurysms should not present insuperable technical difficulties. First because they are primarily "subarachnoid" aneurysms lying free in the subarachnoid space, so that little retraction of brain is necessary to expose them. Secondly both vertebral arteries are visible for most of their course through a posterior fossa approach, and there is a good deal of room for surgical manoeuvre. The whole length of the basilar artery can be clearly seen by a transtentorial approach, the only limiting factor being the fifth, seventh, and eighth cranial nerves which can to some extent be moved out of the way. Finally when treating aneurysms on the vertebral artery and its branches, there is always the opposite vertebral artery to maintain blood flow should it be necessary to occlude the vessel.

Case Material

In view of the rather negative attitude towards surgical treatment, it was felt worth while to record six consecutive cases of ruptured posterior fossa aneurysm operated on successfully.

A second group of six cases selected at random has been included in the series for the purpose of obtaining further examples of the localizing signs of subarachnoid haemorrhage in this situation. Five were obtained from past records at the Atkinson Morley Hospital and are included by kind permission of Mr. Wylie McKissock, and one case came to necropsy at Maida Vale Hospital. It must be stressed that Group II are not to be regarded as a control series medically treated.

The situations of the aneurysms in Groups I and II are shown in Table I.

The cases in Group I are illustrated in line drawings of vertebral arteriograms (Fig. 1).

The vertebral trunk in the region of the origin of the posterior inferior cerebellar artery was the commonest site. No significant predominance with regard to side was shown by the whole series.

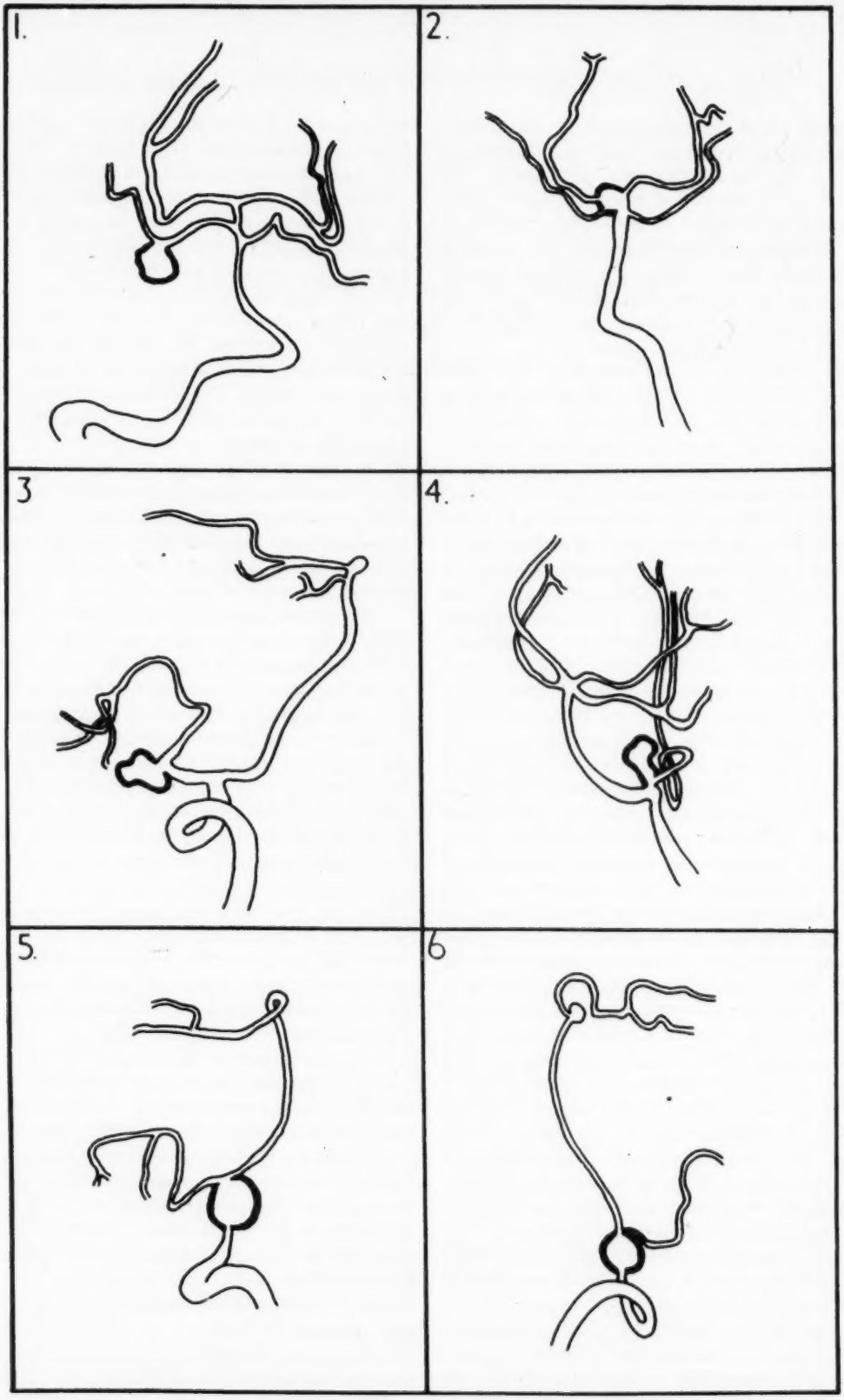

FIG. 1.—Vertebral arteriograms of the six patients submitted to surgery.

Case 1 (*C.G.*).—Antero-posterior projection to show the aneurysm on the right superior cerebellar artery.

Case 3 (*J.R.*).—Lateral view showing a large aneurysm with a broad neck on the posterior inferior cerebellar artery.

Case 5 (*M.K.*).—Lateral view. The aneurysmal sac consists of a dilatation of the vertebral arterial trunk; the posterior inferior cerebellar artery arises from the apex of the aneurysm with the distal trunk of the vertebral.

Case 2 (*C.C.*).—Antero-posterior view. The aneurysm arises from the right side of the basilar artery and gives origin to the posterior cerebral and superior cerebellar trunks.

Case 4 (*C.H.*).—Oblique view to show the bilocular aneurysm arising directly from the vertebral artery in conjunction with the origin of the posterior inferior cerebellar branch.

Case 6 (*P.McM.*).—Lateral view showing the sac which consists of a dilatation of the vertebral artery just within the foramen magnum. The posterior inferior cerebellar artery has the same relationship to the sac as in Case No. 5.

TABLE I

SITE OF ANEURYSMS

	Case	Side	Situation
Group I	1 C.G.	Right	Superior cerebellar artery
	2 C.C.	Left	Basilar at origin of superior cerebellar and posterior cerebral arteries
	3 J.R.	Left	Posterior inferior cerebellar artery
	4 C.H.	Left	Aneurysm arising by neck from the vertebral artery
	5 M.K.	Right	On the vertebral artery as localized saccular dilatation
	6 P.McM.	Left	On the vertebral artery as localized saccular dilatation
Cases 4, 5, and 6 all closely related to the origin of the posterior inferior cerebellar artery			
Group II	7 D.S.	Left	Basilar at origin of superior cerebellar and posterior cerebral arteries
	8 G.S.	Left	Anterior inferior cerebellar artery
	9 V.S.	Middle	Basilar artery
	10 R.R.	Right	Vertebral basilar junction
	11 E.J.	Left	Posterior inferior cerebellar artery
	12 J.D.	Right	Posterior inferior cerebellar artery

Clinical Features

The present series showed a slight female preponderance of eight females to four males (Table II). The ages at time of the subarachnoid haemorrhage ranged from 35 to 68, and eight of the 12 patients were between the ages of 40 and 60, the age period of maximal incidence for this disorder. The sex and age distribution did not differ therefore from that in subarachnoid haemorrhage from supratentorial aneurysms.

TABLE II

CLINICAL FEATURES

	Case	Site of Aneurysm	Bleeds	Disturbance of Consciousness	Fundi	Pupils	External Ocular Movements	5th	7th	8th	Limbs	Plantars	Operation Day Taken since Last Bleed	Result
Basilar	1. C.G. ♀ 56	R. sup. cerebellar	4	1 fit 4 comas			R. 6th	R. pain and sensory loss	L. upper motor neurone	R. deaf	L. hemiparesis		16th	Recovery
	2. C.C. ♀ 49	L. sup. cerebellar Post. cerebral	1	Confused		Dilated					L. upper limb all jerks +	↑ ↓	15th	Recovery
Vertebral Post. Inf. Cerebellar	3. J.R. ♂ 35	L. post. inf. cerebellar	4	1 collapse 1 fit 1 collapse		Transient unequal contracted	Transient nystagmus	Contralateral pain			Weakness legs		2nd	Recovery
	4. C.H. ♀ 50	L. Vertebral	1	Coma 2 hr. Semicoma 12 hr.		R. miosis	Ptosis Transient nystagmus	P.H. L. pain		Vertigo	Weak legs Sensory loss		19th	Recovery
	5. M.K. ♀ 47	R. Vertebral	4	3 fits Coma 1 hr.	Haem. ++		Ptosis	Painful paraesthesiae	L upper motor neurone	Vertigo	R. then L. hemiparesis	↑ ↑	12 hours	Recovery
	6. P.McM. ♂ 55	L. Vertebral	2	Semicoma 36 hr.		Contracted	L. 6th nystagmus				Weak legs L. hemiparesis	↓ ↓ ↑ ↑	10th	Recovery
Basilar	7. D.S. ♀ 53	L. sup. cerebellar Post cerebral	1 in 1954 3	Semicoma Deep 2 hr. Semicoma	Papilloedema	Contracted	Ptosis	P.H. L. pain			Weak legs t onset L. spastic hemiparesis	↑ ↑	Chest infection Death 5th day of illness	
	8. G.S. ♀ 34	L. ant. inf. and sup. cerebellar	3	Coma 12 hr. recovered Uncon. 15 min. Fit 4th day	Haem. and Papilloedema						L. hemiparesis Twitching R. arm		Death 6th day	
	9. V.S. ♀ 52	Mid basilar	1 fatal	Found unconscious		Dilated Unequal Fixed					Flaccid quadriplegia	↓ ↓	Death 10 hours after admission	
	10. R.R. ♂ 43	?R. vert. and basilar	3	1 fit uncon. 30 min. Uncon. 1 hr. on 11th day	Papilloedema				R. upper motor neurone		R. hemiparesis	↑ ↑	Death 26th day	
Vertebral Post. Inf. Cerebellar	11. E.J. ♀ 68	L. vert. and post inf. cerebellar	1	Coma 12 hr.	Haem.	Contracted	Bilateral 6th		R. upper motor neurone	L. deaf	R. hemiparesis		Recovery	
	12. J.D. ♂ 62	R. vert. and post. inf. cerebellar	2	Drowsy ↓ Coma	Haem.	Contracted	Contralateral 6th				Weak legs L. > R.	↑ ↑	Death 7th day	

Symptoms and Signs

Weakness of the Legs.—This or sudden falling was an initial symptom in five patients. The loss of power was not infrequently transient and might improve before the patient was prostrated by headache. One patient (Case 3) stopped driving his car because of leg weakness and nausea before the usual symptoms of subarachnoid haemorrhage developed a quarter of an hour later. Case 6, a man aged 55, after mild headache for four days suddenly vomited and lost the use of his legs. A woman (Case 4) "flopped" to the floor during a dancing lesson because her legs gave way. Another woman (Case 7) was found by her husband holding herself up by the sink, and did not develop headache till some hours later. A man aged 62 (Case 12) suddenly developed weakness of the left leg, which then spread to the right and was followed by headache and vomiting.

Headache.—Headache was an early symptom in every patient except one (Case 8) who lost consciousness immediately and died in coma. A period of mild headache for several days might be followed by a severe exacerbation with signs of meningeal irritation, indicating a frank haemorrhage. The intense headache was usually occipital at the onset but then became generalized, spreading over the head to the frontal region. The accompanying neck rigidity was usually of moderate degree, and head retraction was exceptional. Localization of pain in the region of the ear on the same side as the aneurysm was observed in two patients, in one (Case 1) associated with an aneurysm on the superior cerebellar artery, and in the other (Case 5) with an aneurysm on the vertebral artery. A past history of frontal headache regarded as migraine was given by three patients (Cases 1, 4, and 5). Case 4 had experienced trigeminal neuralgia on the side of the aneurysm. Sensory disturbance in the trigeminal territory in Cases 1 and 5 accompanied actual rupture. However, lateralization of the aneurysm by the site of the pain at the onset of haemorrhage was not always reliable. One man, aged 35 (Case 3), had experienced right-sided headache for a month, and at the time of the ictus complained of an intense exacerbation, but the aneurysm was situated on the left vertebral artery.

Loss of Consciousness.—The initial loss of consciousness might be of sudden onset and of up to 36 hours' duration followed by recovery of the senses. The patient then might become alert and cooperative (Cases 3, 8, and 11). A noticeable feature of the disorder in seven patients was that of brief depressions in the level of consciousness, followed by rapid improvement, and five of these patients (Cases 1, 3, 5, 8, and 10) also experienced convulsive episodes.

A woman, aged 47 (Case 5), had an epileptiform attack with jerking movements of the arms and stertorous breathing at the onset of the haemorrhage, and later in her illness two generalized convulsions with "bubbly" respiration, followed by a transient flaccid hemiplegia. One man (Case 3) lost consciousness on the eighth day of illness with frothing at the mouth. Later on the same day, on recovery from anaesthesia for carotid and vertebral angiography, he collapsed again with slow stertorous breathing. The pupils were contracted and both plantar responses became extensor. The supraorbital nerve was compressed to assess the depth of coma, at which stimulus he suddenly showed free movement of the limbs, recovered consciousness, became loquacious and said he felt fine. Presumably on this occasion the rapid change in his condition was due to spasm of the basilar artery, followed by return of the circulation. Stertorous respiration and hypersecretion of mucus were prominent in these attacks, and were also observed in another patient (Case 10) accompanied by protrusion of the tongue. A focal adversive attack occurred in one patient, and focal seizures in the arm in another with evidence of fresh haemorrhage.

Recurrent Haemorrhage.—Recurrences of haemorrhage, as judged by increase of headache, deterioration in the level of consciousness, and fresh blood in the cerebrospinal fluid were a common feature of these aneurysms, and eight patients (Cases 1, 3, 5, 6, 7, 8, 10, and 12) together had 25 haemorrhages. A fatal outcome or crippling neurological disability did not necessarily result. Three patients (Cases 1, 3, and 5) each had four haemorrhages, yet survived operation.

Fundus Oculi.—Retinal or subhyaloid haemorrhages were seen in four patients (Cases 5, 8, 11, 12). One woman (Case 5) had gross bilateral subhyaloid haemorrhages due to a subarachnoid haemorrhage from a right vertebral aneurysm. Papilloedema was present in three patients (Cases 7, 8, and 10), one of whom (Case 8) showed papilloedema on the same side as the haemorrhage and a vitreous haemorrhage in the other eye.

Cranial Nerve Signs.—Abnormalities of the pupils and ocular movements were the commonest defect of the cranial nerves. Bilateral contraction of the pupils was observed in five patients (Cases 3, 6, 7, 11, and 12) and unequal pupils in three (Cases 3, 4, and 9). Two patients (Cases 2 and 9) showed widely dilated pupils which were also inactive in the latter

patient (Case 9) who subsequently died. Sixth nerve palsies, which might be unilateral or bilateral, occurred in four patients (Cases 1, 6, 11, and 12). When unilateral, the palsy was not of value as a lateralizing sign unless associated with palsies of neighbouring cranial nerves as in one patient (Case 1) with trigeminal and eighth nerve lesions in addition. Three patients showed ptosis (Cases 4, 5, and 7), and three (Cases 3, 4, and 6) nystagmus which appeared at the onset of the haemorrhage as a transient feature, but was sustained in one patient (Case 6) on lateral deviation towards the side of the lesion, a vertebral aneurysm.

Paraesthesiae in the trigeminal territory in one patient (Case 5), and cutaneous sensory loss in another (Case 1) developed on the same side as the ruptured aneurysm. Symptoms referable to the eighth nerve consisted of rotatory vertigo (Cases 4 and 5), and two other patients (Cases 1 and 11) became deaf on the side of the ruptured aneurysm.

A contralateral facial paresis of an upper motor neurone type was observed in four patients (Cases 1, 5, 10, and 11) associated with a hemiparesis.

Signs in the Limbs.—These were bilateral in 10 patients (Cases 1, 2, 4, 5, 6, 7, 8, 9, 10, and 12). Evidence of pyramidal disturbance was found in all the patients at some time in their illness, though in one (Case 3) only after a fit when bilateral extensor plantar responses appeared. Weakness of the legs as mentioned before occurred as an initial symptom in five patients.

A unilateral hemiparesis (Cases 6, 8, 10, and 11) or alternating hemiparesis (Cases 5 and 7) might appear in association with a sudden loss of consciousness or convulsive episode. These hemipareses were often transient leaving only slightly increased tendon reflexes. A total flaccid paraplegia was present until death in a haemorrhage due to rupture of a mid-basilar aneurysm. The plantar response was extensor in character in 10 patients, and in seven of these the abnormality was bilateral. A "crossed" paralysis or hemiplegia was observed in two patients (Cases 1 and 11) with cranial nerve lesions on one side and pyramidal signs in the opposite limbs. Sensory loss in the limbs, as in most cases of subarachnoid haemorrhage was uncommon; one patient (Case 4) showed impaired appreciation of temperature contralaterally and absent vibration sense in the leg on the side of a vertebral aneurysm.

Investigations

The cerebrospinal fluid pressure in the early hours after the subarachnoid haemorrhage was available in nine cases. The level was not of a high order initially, and in five patients was 200 mm. or less, though later, especially in the fatal recurrences, levels of 300 mm. and over developed (Table III).

TABLE III
CEREBROSPINAL FLUID PRESSURE

C.S.F. Pressure in mm.	Case No.
Normal	5 and 7
150 to 200	2, 6 and 8
210 to 250	1, 3, and 12
300	10

Although subhyaloid haemorrhages are usually attributed to haemorrhage from an anteriorly situated aneurysm, or to a sudden rise in cerebrospinal fluid pressure sufficient to occlude the central retinal veins, there did not seem a correlation between the presence of these changes in the fundi and the cerebrospinal fluid pressure at lumbar puncture. Widespread subhyaloid haemorrhages were present in both eyes in one patient (Case 5) when the cerebrospinal fluid pressure was 140 mm. Another (Case 8) showed a right vitreous haemorrhage and left-sided papilloedema with a cerebrospinal fluid pressure of 200 mm.

Electroencephalography (E.E.G.).—Electroencephalographic recordings were carried out in four patients (Cases 2, 3, 4, and 5). Similar E.E.G. abnormalities were observed in those patients (Cases 2, 4, and 5) with haemorrhage due to rupture of an aneurysm arising close to the basilar-vertebral trunk. The abnormalities consisted of periodic bursts of generalized slow waves in the frontal and occipital leads occurring at intervals of 10 to 60 seconds and lasting one to two seconds. The amplitude of the slow-wave bursts was greatest in Case 2, a patient with a relatively small aneurysm, but which arose directly from the anterior end of the basilar artery.

The phenomenon of periodic bursts of generalized slow waves has been described by other authors including Tucker (1958) in lesions of the brainstem.

Radiology.—Bilateral carotid angiography was employed in 11 patients without revealing the aneurysm, and right carotid angiography repeated on another occasion in Case 1 showed no abnormality. In Group I unilateral vertebral angiography, lateralized on clinical features in three patients (Cases 1, 5, and 6), filled the aneurysm successfully. Bilateral vertebral angiography was required in three patients. In Case 2 vertebral angiography on one side was unsuccessful, but the basilar aneurysm filled satisfactorily from the other vertebral. In Case 3, a man with severe right-sided facial pain, the right vertebral artery was injected first due to the

false localization by facial pain and the basilar artery filled without showing the aneurysm on the left posterior inferior cerebellar artery. In Case 4, spasm of the intracranial vessels and irregularity of the right vertebral artery was observed but injection of the opposite vertebral artery revealed the aneurysm on the left posterior inferior cerebellar artery.

Post-operative angiography in Group I was carried out, except in those patients where proximal ligature of one vertebral artery had been employed (Cases 5 and 6), as spasm of the remaining patent vertebral artery might well have endangered the basilar circulation.

Vertebral angiography was performed in two patients (Cases 10 and 11) in Group II; in Case 10 the result was equivocal, in Case 11 bilateral vertebral angiography showed a tortuous basilar artery and a small aneurysm on the left posterior inferior cerebellar artery.

Ventricular dilatation was observed in three patients (Cases 3, 7, and 11). Wide-swept anterior cerebral arteries on carotid angiography in Case 7 indicated enlargement of the ventricles. Ventriculography in Case 3, a man aged 35, who developed ataxia and dementia after subarachnoid haemorrhage from a posterior inferior cerebellar aneurysm, showed generalized ventricular dilatation due to a communicating hydrocephalus. A slight ventricular dilatation was found in Case 11, a woman aged 68, on whom air studies were carried out to exclude the presence of a clot when a hemiparesis developed.

Carotid angiography, although it might reveal a complicating ventricular dilatation, was not of assistance in visualizing these aneurysms. If unilateral vertebral angiography was negative in Group I cases, the opposite vertebral artery was injected; otherwise it was found that an aneurysm on a vertebral artery at the usual site in proximity to the origin of the posterior inferior cerebellar artery might be missed.

Ventriculography was required to detect the presence of hydrocephalus resulting from interference with circulation of cerebrospinal fluid by adhesions in the posterior fossa.

Surgery of Posterior Fossa Aneurysms

The principles of surgical treatment of aneurysms in this location are similar to those which apply to the supratentorial aneurysms. Thus the method of election consists of the occlusion by clip or ligature of the neck of the aneurysm without interference with the patency of the parent vessel, as was achieved in Cases 3 and 4. When the aneurysm arises from what is considered to be an expendable artery the sac with its segment of vessel may be completely excised, as in the case reported by Schwartz in 1948 and in Case 1 of this series. The related procedure of "trapping" the aneurysm by a clip on the artery, both proximal and distal to the origin of the sac, is also a feasible one for dealing with saccular dilatations of the vertebral artery. This method was considered for Cases 5 and 6, but the fact that in both these patients the posterior inferior cerebellar artery took origin directly from the apex of the sac precluded the manoeuvre. A clip on the vertebral artery proximal to the sac had to suffice, and was successful in preventing further bleeding.

Some doubt has been cast on the efficacy of this method of proximal occlusion of the vertebral artery for saccular dilatations of its trunk by the experimental work of Bakay and Sweet (1953) and has been quoted by other authors. Their investigation consisted of acute experiments (the number of which was not stated in the article) carried out during the course of operations on patients with posterior fossa lesions. The vertebral artery was occluded outside the skull between the occiput and atlas, measurements of the blood pressure then being recorded from the vertebral artery and posterior inferior cerebellar artery, using a very fine needle and electromanometer. The authors concluded that ligation of the vertebral artery on one side did not produce an adequate drop in pressure in the vessel for treatment of an aneurysm providing the opposite vertebral trunk was of approximately the same size.

Whether the results of brief occlusions of the vertebral artery in patients under full anaesthesia can be compared with the long-term pressure changes following vertebral clipping in patients with normal vascular tone, or even increased tone following a subarachnoid haemorrhage, is open to serious question.

Certain practical observations made at operation in the present series are relevant to this discussion. Thus when the vertebral artery is clipped, the aneurysmal sac is left situated at the end of a long cul-de-sac in which the blood flow is reversed. At operation on the two patients in this series (Cases 5 and 6) when the vertebral artery was occluded the aneurysmal sac was seen to decrease considerably in size and the amplitude of its pulsation diminished. In both patients following this procedure ischaemic brain-stem symptoms developed and there can be no greater proof than this that proximal occlusion influenced the blood supply. Finally in both the patients there has been no repetition of the haemorrhage post-operatively, and one of them had had repeated severe bleeds.

It would seem therefore from actual surgical experience that occlusion within the skull of a vertebral artery proximal to a ruptured saccular dilatation is an effective method of treatment, and

that in practice the real danger lies in the production of an excessive fall in blood pressure with subsequent ischaemia of the brain-stem, although it was recoverable in both these patients. The risk of thrombosis of the basilar artery following vertebral ligation must be mentioned, as this has been considered a contraindication by DeSaussure and his colleagues (1958). The recent case discussed by them in which this complication occurred was described by French and Haines (1950) and was not comparable, as the vertebral-basilar circulation was hypertrophied to supply a vascular meningioma.

Another method of treatment consists of wrapping a sheet of muscle round the aneurysm. This technique was adopted in Case 2, because both the posterior cerebral and superior cerebellar arteries on the same side were found to arise from the sac, and it was considered that occlusion of the aneurysm with these two vessels carried too high risk of infarction. If for anatomical reasons other methods are not practical, this procedure may occasionally be indicated.

Surgical Approach.—The six patients in this series were all operated upon in the sitting position in a surgical chair utilizing conventional anaesthetic technique, except for Case 4, the most recent case chronologically, in which hypothermia was also induced.

Two methods of surgical approach were adopted.

Aneurysms on the vertebral arteries and their branches were explored through a unilateral posterior fossa craniectomy, and even in Case 4 where the sac was shown by arteriography to be situated far anteriorly in the fossa, relatively little difficulty in access was experienced.

On the other hand, aneurysms on the basilar and superior cerebellar artery were visualized by a transtentorial approach. This was carried out through a craniotomy flap exposing the posterior, temporal, and occipital regions. This area of brain was then elevated, as far as possible preserving the veins draining into the superior petrosal sinus, the tentorium then being incised a few millimetres behind its petrous attachment and avoiding damage to the fourth nerve. On retracting the cerebellar hemisphere the basilar artery and its branches could then be clearly seen, the only obstruction to exposure being the fifth, seventh, and eighth cranial nerves, and in Case 1 the fifth nerve had to be divided in order to mobilize the sac on the superior cerebellar artery.

One disadvantage of this approach was that a homonymous hemianopia invariably resulted, but cleared up in one to three weeks.

Time for Surgery.—The principle that arteriography and operation should be performed as soon after the haemorrhage as the patient's condition permits was followed as far as possible. However, as will be seen from Table IV, the time that elapsed between the last haemorrhage and operation varied from 12 hours in Case 5 to 19 days in Case 4. The longer intervals were mainly caused by the wait between the performance of the carotid and the vertebral arteriograms, and in three of these six patients it should be noted that further haemorrhages occurred during this interval.

Early diagnosis is important in the management of these patients. Ruptured posterior fossa aneurysms bleed repeatedly and are dangerous due to the risk of infarction of the pons, haemorrhage into the brain-stem and cerebellum, and organization of blood clot in the posterior fossa. Although

TABLE IV

OPERATIVE RESULTS

Case	Day of Illness	Interval since Last Bleeds	No. of Bleeds	Condition at Operation	Convalescence	Interval	Activity	Residual Defects
1. C.G.	21st	16 days	4	Good	Uninterrupted	7 years	Full	5th sensory loss following section at operation. Slight contracture homolateral facial muscles
2. C.C.	15th	15 days	1	Good	Uninterrupted	18 months	Full	None
3. J.R.	9th	2 days	4	Poor	Dementia due to communicating hydrocephalus	2 years	Light work	Nystagmoid jerks. Slight difficulty in balancing on one leg
4. C.H.	19th	19 days	1	Good	Uninterrupted	1 year	Full	Initial weakness of left trapezius
5. M.K.	9th	12 hours	4	Poor	Difficult. Brain-stem ischaemia. Tracheotomy	18 months	Impaired	Low visual acuity. Ataxia of gait
6. P.McM	10th	10 days	2	Fair	Difficult Brain-stem ischaemia Tracheotomy for respiratory infection	2 years	Light work	Horizontal nystagmus Reduction of cutaneous sensibility below knee of R. leg. Joint sense impaired in toes

the disturbances of consciousness and limb pareses may be transient, the patient's mentality and general condition deteriorate with each bleed and chest infection tends to supervene.

Cases 3 and 5 were operated on the ninth day of illness, the former two days and the latter 12 hours after a fourth haemorrhage. Both were gravely ill at the time of operation and had difficult post-operative periods. Case 3 remained confused with marked intellectual deterioration due to a communicating hydrocephalus which required anterior ventriculostomy. Some circulatory disturbance may already have been present in Case 5 as she had had two convulsions with bubbly respiration and transient hemipareses 12 hours before operation. She developed symptoms of bulbar ischaemia post-operatively from which she made a slow recovery and was left with some ataxia of gait. Visual failure due to subhyaloid haemorrhages is another danger of delay, but in Case 5 the damage occurred after the first haemorrhage.

Even in gravely ill patients the level of consciousness and vital functions after a bleed usually recover to a stage at which neurosurgery can be undertaken. Repeated lumbar puncture may be useful.

As will be seen from the abstract of results (Table IV) good condition at the time of operation and absence of significant cranial nerve or other pareses are the features which assist in obtaining a satisfactory operative result.

A greater awareness of the clinical features of haemorrhage due to posterior fossa aneurysms would lead to the diagnosis being suspected at an earlier stage, so that vertebral angiography could be employed without unnecessary delay. The problem whether carotid angiography can be omitted in selected cases will be considered in the discussion.

Discussion

Certain clinical features of the ictus require explanation, such as the absence of signs of cerebellar disturbance, apart from nystagmus, when an aneurysm associated with one of the cerebellar arteries has ruptured. Elkington (1958) has attributed the rarity of frank cerebellar symptoms in basilar occlusion to the rich anastomoses between several vessels in this organ or because of its relative insensitivity to anoxia. Perhaps in aneurysmal lesions previous ischaemia in the territory of the affected vessel has resulted in the opening up of collateral supplies, or compensatory mechanisms have developed as in other slowly growing cerebellar lesions. The midline cerebellar syndrome with truncal ataxia might not be detected in these seriously ill patients who cannot be mobilized.

Kremer (1958) regards weakness and collapse of the legs at the onset as a manifestation of disturbance of the cerebellar connexions in the brain-stem knocking out the Y-fibre servo loops.

The severity of the subhyaloid haemorrhages may be surprising as the source of the bleeding is posteriorly situated and the cerebrospinal fluid pressure is not invariably high. It is important to realize their occurrence, otherwise delay in diagnosing posterior fossa aneurysms may result from repeated carotid angiography or attempts to find other causes, such as a haemorrhagic diathesis, before vertebral angiography is undertaken.

Haemorrhage in the posterior fossa may produce some form of block so that the cerebral and spinal subarachnoid pressures do not equalize. Taylor and Whitfield (1936) described a case in which no blood reached the cerebrospinal fluid and suggested that sudden bleeding might result in a cerebellar pressure cone. Swelling of the cerebellum also can be associated with vascular disturbances of the lateral tegmentum of the pons as observed by Atkinson (1949) in operative occlusion of the anterior inferior cerebellar artery. Such mechanisms, however, have only been seen in fatal cases. The brain in Case 7 showed multiple infarctions in the pons, some of which were situated in the lateral tegmental region, dilatation of the lateral ventricles previously diagnosed by carotid angiography before death, blood in the fourth ventricle, and grooving of the cerebellar tonsils suggestive of herniation (Figs. 2, 3, and 4).

Ventricular dilatation may result from the presence of firm blood clot in the fourth ventricle and subarachnoid space, and in the course of a week or so adhesions form in the posterior fossa as displayed at operation in Cases 3 and 4. In the former patient (Case 3) operative treatment was required to short circuit the obstruction by a ventriculostomy.

The true incidence of posterior fossa aneurysms is difficult to determine until bilateral vertebral angiography is carried out as a routine in cases of subarachnoid haemorrhage, when carotid angiography is negative. If the incidence is of the order of 10 to 15%, as has been suggested, it would seem high enough to justify complete angiography. It will be realized that vertebral angiography will of course show up vascular lesions in the peripheral distribution of the vertebral supply beyond the subtentorial area to which this communication is confined, namely, the posterior cerebral trunks and their branches in the occipital lobes. The importance of this wider aspect of the investigation of patients with subarachnoid haemorrhage was emphasized by Spatz and Bull (1957) when, in 60 patients in whom bilateral carotid angiograms showed no lesion,

FIG. 2

FIG. 3

FIG. 4

FIG. 2.—Case 7. Section of brain-stem at mid-pontine and nodular level to show multiple pontine infarcts, and two infarcts in left cerebellar hemisphere with blood in fourth ventricle.

FIG. 3.—Case 7. Section of brain showing dilatation of anterior and posterior horns of lateral ventricles.

FIG. 4.—Case 7. Atheromatous basilar artery with aneurysm situated between left posterior cerebral and superior cerebellar arteries. Grooving of cerebellar tonsils.

subsequent vertebral angiography showed a vascular cause in 16 cases (26%) of which eight were angiomas and eight aneurysms.

The question arises whether the clinical features of aneurysms in the posterior fossa are sufficiently clear cut to justify vertebral angiography without undertaking bilateral carotid puncture first. Onset with weakness of the legs, fluctuations in consciousness, convulsive attacks with respiratory disturbances and hypersecretion of mucus, and minor brain-stem signs seem characteristic of subarachnoid haemorrhage due to these lesions, and recurrence of haemorrhage is common in the first three weeks. The difficulty is to distinguish between the disturbances due to haemorrhage in the region of the posterior fossa from those due to ruptured aneurysm of the anterior cerebral anterior communicating artery, which is a commoner cause of subarachnoid haemorrhage and is responsible for about 26% of cases. The anterior cerebral anterior communicating and basilar-vertebral aneurysms share in common certain clinical features, as haemorrhage from either irritates the brain-stem, though at different levels. Irrecoverable signs of neurological damage are commoner in the anteriorly situated aneurysms but time only can prove this in the individual patient. Both show the features of recurrent bleeds, and fluctuations in the level of consciousness. Unless neighbourhood signs in the cranial nerves indicate without doubt the lesion in the posterior fossa, the difference in incidence is so considerable that it would seem essential to carry out bilateral carotid angiography as an initial investigation. However, delay before proceeding to vertebral angiography should be minimal as a fatal bleed may occur any time in the posterior fossa, or irrecoverable damage to vision result if subhyaloid haemorrhages are prominent. An important point is that vertebral angiography should be bilateral, as although the basilar artery can be filled satisfactorily from either vertebral artery, unless both vertebral arteries are injected an aneurysm at the origin of the posterior inferior cerebellar artery may be missed.

The view has been expressed by Walton that vertebral angiography has the disadvantage of a higher incidence of thrombotic incidents which may be fatal. In the first six cases under consideration, angiography of carotid and vertebral vessels was carried out by a skilled radiologist. A sudden collapse with stertorous breathing followed combined carotid and vertebral angiography in Case 3, but on a painful stimulus he immediately recovered consciousness without any sequelae.

The prognosis of an individual haemorrhage is less grave than might be expected from the clinical features. Manifestations usually considered to indicate a poor prognosis, such as convulsions, stertorous breathing, and long tract signs, may be produced by irritation of the brain-stem without irrecoverable neurological damage, so have a less grave significance than when resulting from aneurysms elsewhere. The bilateral supply at the posterior and anterior extremity of the basilar artery may help to maintain the circulation.

Surgical treatment would seem the only effective answer to subarachnoid haemorrhage in the posterior fossa. The condition has a high natural mortality due to recurrent bleeds and spontaneous recovery took place only in one elderly patient (Case 11) in this series of 12 cases. Nothing therefore can be lost by embarking on vertebral angiography when carotid angiography is negative. If the lesion proves operable the results are good in experienced hands, even in the patients gravely ill from recurrent haemorrhages at the time of surgical intervention.

Conclusions

Twelve cases of subarachnoid haemorrhage due to posterior fossa aneurysms are described. The incidence shows the same sex and age distribution as in supratentorial lesions.

The clinical features of ruptured subtentorial aneurysms include weakness of the legs at the onset followed by headache and vomiting, fluctuation in the level of consciousness, with stertorous breathing and fits. Cranial nerve signs consist of subhyaloid haemorrhages, contracted pupils, nystagmus, and fifth, sixth, seventh, and eighth nerve pareses. Transient hemipareses occur in the limbs, sometimes with bilateral pyramidal signs. Electroencephalography (E.E.G.) may be of value by recording periodic bursts of slow waves suggestive of a brain-stem lesion. Both vertebral arteries may require injection to detect the aneurysm. The lesions are dangerous because bleeding usually recurs unless surgical treatment is undertaken. All six patients, on whom craniotomy was performed with suitable operative treatment of the aneurysm, survived, and five of the six made good recoveries. Hydrocephalus may occur as a complication.

CASE HISTORIES

Group I

Surgical treatment was used in Cases 1 to 6.

Case 1.—C.G., a woman aged 56, who had suffered from migraine all her life, experienced a sudden backache after which she became stiff and her eyes turned inwards. On coming round she complained of pain in the neck and right ear. She then vomited and developed neck stiffness so she was thought at first to have meningitis.

Neurological Examination.—The patient just responded to her name and painful stimuli. Neck rigidity was well marked. The right corneal reflex was diminished and both plantar responses were extensor.

The cerebrospinal fluid pressure was 250 mm., and the fluid was heavily bloodstained. A right carotid angiogram showed no abnormality.

Course.—Two further coma-producing bleeds occurred with increased evidence of neurological damage. Examination in the third week showed a right sixth nerve paresis, hyperpathia in the first and second division of the right trigeminal nerve, and hypalgesia over the third division, deafness of the right ear, and a left upper motor neurone facial palsy with a left hemiparesis. Open right carotid and right vertebral angiograms were performed; the latter radiograph revealed an aneurysm on the right superior cerebellar artery.

Operation (V.L.).—This was performed on the sixteenth* day by the transtentorial approach. The tentorium was incised up to its free margin. An aneurysm 1 cm. in diameter, lying immediately medial to the fifth nerve in a mass of clot, was found on the right superior cerebellar artery. The fifth nerve had to be divided to provide access. The artery was clipped on either side and the aneurysm excised.

Post-operative Progress.—The patient made an uninterrupted convalescence. Now six years later she leads a perfectly normal life, doing housework and shopping. She has never had another attack of migraine. Residual signs are those of right fifth nerve anaesthesia and slight contracture of the facial muscles on the same side.

The cessation of attacks of "migraine" suggest that the pain resulted from compression of the trigeminal nerve by the aneurysm. The intense pain in the right ear might be the result of disturbance of the nervus spinosus. This patient was the first in the series and vertebral angiography was performed late. The course shows the capacity for a patient to survive repeated haemorrhage around the brain-stem with recovery from a crossed hemiparesis. An important factor seems to be the absence of arteriosclerosis so that disturbances of the basilar circulation do not result in infarction of the pons.

*Time interval between most recent haemorrhage and operation.

Case 2.—C.C., a woman aged 49, suddenly developed stiffness of the neck and back. She felt ill and so went into her neighbour's house where she vomited and complained of severe headache. Initially the pain was suboccipital in position but later spread forwards and became generalized.

Neurological Examination.—The next day she was confused, with neck rigidity, dilated pupils, and increased tendon jerks. The cerebrospinal fluid was at a pressure of 200 mm. and was bloodstained. On admission to Maida Vale Hospital the pupils were widely dilated and responded poorly to light and accommodation. There was a slight spastic weakness of the left arm, and a generalized increase of the tendon jerks, maximal in the left arm. The left plantar response was flexor, but the right was extensor; the signs therefore suggested a bilateral lesion.

The electroencephalogram showed periodic synchronous outbursts of high-voltage slow activity, less in amplitude on the right side, suggesting anterior diencephalic compression.

Angiography.—Bilateral carotid angiography was negative. Right vertebral angiography showed spasm with no intracranial filling. Left vertebral angiography revealed a small saccular aneurysm at the upper end of the basilar artery giving rise to both superior cerebellar and posterior cerebral arteries.

Operation.—Operation (V.L.) on the fifteenth day by the subtemporal route confirmed that the aneurysm was situated exactly as the arteriogram had suggested. The sac was lying medial to the origin of the third nerve. Owing to the possibility of widespread ischaemia if the aneurysm was clipped across its base, it was packed around with muscle.

Post-operative Progress.—The patient had an uneventful convalescence and was leading a normal life without residual signs one year after the operation.

This procedure, although not radical, has been effective in preventing recurrence of the haemorrhage for the past 18 months.

Case 3.—J.R., a man aged 35, a motor mechanic, had experienced a right-sided posteriorly situated headache for four weeks. When driving his van objects suddenly looked out of focus, he felt cold, sick, and weak in the legs. He was unable to drive so stopped and opened the windscreen. He proceeded for another quarter of a mile when he was overcome by severe right-sided headache with vomiting but did not lose consciousness.

Neurological Examination.—There was neck rigidity, the right pupil at first was larger than the left, but the next day both pupils became contracted. The cerebrospinal fluid was at a pressure of 250 mm. and was bloodstained.

The electroencephalogram (E.E.G.) was of rather low

voltage, and the alpha rhythm was poorly developed. Periodic slow activity occurred in both occipital regions suggesting an occipital abnormality, possibly related to an aneurysm.

Course.—Bilateral carotid angiography was negative in the first week. Two further bleeds occurred subsequently, the second resulting in loss of consciousness for a few minutes with frothing at the mouth. On recovery he complained of an increase in headache and neck stiffness. Lumbar puncture showed an increase in pressure and fresh blood in the cerebrospinal fluid. A repeat left carotid angiogram 12 hours later was negative and a right vertebral angiogram showed poor filling of the basilar artery. Left vertebral angiography was then proceeded with and demonstrated an aneurysm arising from the posterior inferior cerebellar artery just above the posterior margin of the foramen magnum in the midline.

While still under the anaesthetic after angiography his respiration became stertorous and infrequent, so an endotracheal tube was passed. The respiratory rate went down to 8 per minute, the pupils were contracted but remained active, and the plantar responses became extensor in character. On stimulation of the supraorbital nerves there was free movement of the limbs, the patient became loquacious and said he felt fine. He made a rapid recovery from the anaesthetic, and the cerebrovascular spasm appeared to have passed off, but a further bleed occurred in the night.

Operation.—Operation was performed (V.L.) on the second day using a midline incision.

A bilocular aneurysm measuring 15 × 7 mm. was found arising from the left posterior inferior cerebellar artery lying between the cerebellar tonsils. The sac was mobilized and ligated, leaving a small vestibule joining the entry and exit vessels so as to avoid occluding them. The artery was such a large one that it was considered unwise to excise the segment of vessel bearing the aneurysm.

Post-operative Progress.—The patient developed dementia and ataxia due to a high pressure communicating hydrocephalus with a block at the tentorium and ventricular dilatation demonstrated by ventriculography. The condition was treated by anterior ventriculostomy.

One year later, his intellect and personality were said to be normal, the only abnormal signs being nystagmoid jerks and a little difficulty in balancing on one leg. He returned to light work with his original firm.

Pain in the head on the opposite side to the aneurysm proved a false localizing sign in this patient's case.

Case 4.—C.H., a woman aged 50, many years ago suffered an attack of left trigeminal neuralgia. She also had experienced two episodes of severe vertigo and headache, 18 and 12 months before the present illness. The first symptom was the sudden onset of weakness during a dancing lesson, so that she "flopped" to the ground and then developed occipital headache. She managed to get off the floor, and sit down on a chair but then lost consciousness for about two hours. On recovery she was aware of a sense of rotation and could not see anything although she realized that people were round her. She had a hazy memory of the rest of the night. At 6 a.m. she had to be dragged across the floor, and was helped into a car to take her home, where on arrival she was given an injection for migraine.

On admission to the local hospital the same day, she was complaining of severe headache, photophobia, and left sciatic pain.

Neurological Examination.—She showed neck stiffness, a contracted right pupil but minimal nystagmus on lateral deviation to the right. There was impaired vibration sense in the left leg and the left plantar response was extensor. Lumbar puncture showed a bloodstained fluid, but the pressure was not available.

Course.—After transfer to Maida Vale Hospital on the eighth day of illness there was slight neck stiffness. The cranial nerves were normal. Repetitive movements of the left hand and left leg were impaired, with ataxia in the heel-shin test. There was impaired vibration sense at the left internal malleolus, and some diminished appreciation of temperature in the right foot. The left plantar response was a weak extensor.

The electroencephalogram showed bursts of mixed theta and slow activity often bilateral, but always more marked on the left, and focal about the central regions.

Bilateral carotid angiography was normal. A right vertebral angiogram showed an irregularity of the right vertebral artery, suggestive of atheromatous involvement between atlas and axis. Left vertebral angiography revealed a saccular aneurysm about the origin of the posterior inferior cerebellar artery.

After angiography a right Horner's syndrome reappeared. The reflexes were reduced; the left plantar was a doubtful extensor. Later a slow nystagmus developed on lateral deviation to the left.

Operation.—Operation was performed (V.L.) on the nineteenth day under hypothermia, the patient in the sitting position.

Thick bands of arachnoid were found binding the ninth, tenth, and eleventh nerves to the seventh and eighth on the left side. A bilocular aneurysm indenting the pons arose by a neck from the left vertebral artery in juxtaposition to the posterior inferior cerebellar artery. The neck of the sac was occluded by a large clip leaving the posterior inferior cerebellar artery intact.

Post-operative Progress.—Angiography showed the clip in position. By 10 weeks after operation the patient was able to do her own housework and drive a car. Her only disability was some weakness in the left sternomastoid and trapezius muscles due to a spinal accessory paresis, which subsequently cleared up.

Case 5.—M.K., a woman aged 47, had suffered from frontal headaches all her life, usually associated with the monthly periods. Four days before admission she wakened with an unusually severe frontal headache. The following day she experienced a "cold ache" at the back of the right ear. Later the same day she felt dizzy, and became unconscious with stertorous respiration and jerking of the arms. On recovery of consciousness an hour later she complained of severe headache and pins and needles in both legs.

Neurological Examination.—There was marked neck rigidity. Severe subhyaloid haemorrhages were present in both fundi, with a bilateral central field defect and reduction of visual acuity to counting fingers. There was bilateral ptosis. The tendon reflexes were increased, more on the right side, the right plantar response was extensor, the left was equivocal. The cerebrospinal fluid pressure was 140 mm. and the fluid was heavily blood-stained.

The electroencephalogram (E.E.G.) was abnormal. The record showed no alpha activity. The most prominent feature was periodic runs of slow-wave activity predominantly frontal and very often focal in the left anterior temporal region.

Course.—Bilateral carotid angiography showed no abnormality. After a transient improvement for two days she suddenly had a generalized convulsion with stertorous, bubbly respiration, followed by a left hemiplegia, maximal in the leg. Some improvement in the hemiplegia took place followed by a further generalized convulsion. Both of these fits were associated with the presence of fresh blood in the cerebrospinal fluid. Right vertebral angiography revealed an aneurysm of the right vertebral artery.

Operation.—At operation 12 hours afterwards (V.L.) a saccular aneurysm 15 × 8 mm. was found on the right vertebral artery immediately after its entry into the cranial cavity. The proximal portion of the vertebral artery was occluded by a single tantalum clip.

Post-operative Course.—The patient developed a bulbar palsy following operation, probably due to ischaemia, which required tracheotomy. She made a slow recovery but nine months after operation she was able to do housework.

Residual signs consisted of wasting of the right side of the tongue, a right Horner's syndrome, and slightly increased jerks on the left side with ataxia of gait. The visual acuity of the left eye improved to J 18; the visual acuity of the right eye was counting fingers.

Case 6.—P.McM., a man 55, had a mild headache for four days which then suddenly became much worse. He vomited, was unable to use his legs, and gradually became semi-comatose.

Neurological Examination.—He could be aroused by verbal stimuli. Neck stiffness was minimal. The pupils were small but reacted to light, there was a left external rectus paresis. Movement was present in the limbs, and also a response to painful stimuli. Tone and tendon reflexes were increased in the left upper limb. The cerebrospinal fluid pressure was 150 mm., with a blood-stained fluid. Bilateral carotid angiograms were negative. A left vertebral angiogram showed an aneurysm on the left vertebral artery, and spasm of the basilar artery.

Operation.—At operation on the tenth day (V.L.) an extensive subdural haematoma was evacuated, and the aneurysm was found arising as a saccular dilatation of the left vertebral artery, immediately after its entry into the skull. The distal portion of the vertebral and the posterior inferior cerebellar artery arose from its apex. The vertebral artery was completely occluded with a clip proximal to the sac.

Post-operative Course.—The day after operation he became stuporose, and developed a more marked left hemiparesis and dysphagia. A tracheotomy was required for the chest infection. He then made a steady recovery in spite of marked ataxia of gait which ultimately cleared up.

Left vertebral angiography showed good filling of the vertebral artery up to about 1 cm. proximal to the clip. No filling of the aneurysm was obtained.

Fifteen months after operation residual signs consisted of a fine horizontal nystagmus, with reduction of appreciation of pain, temperature, and touch in the right leg below the knee, and reduction of joint sense in the toes. He was working full time on light work.

Group II

No surgical treatment was carried out in Cases 7 to 12.

Case 7.—D.S., a woman aged 53, had suffered from headaches all her life, which during the last six years had been severe and stabbing in character, situated on the left side of the head. Ten years ago she had a loss of consciousness, and three years ago a proven subarachnoid haemorrhage.

She was found by her husband looking pale, and hanging on the sink to support herself. Later she developed severe occipital headaches and vomited.

Neurological Examination.—She was drowsy but co-operative. The fundi showed early papilloedema, the pupils were contracted, and she had a slight left spastic hemiparesis with bilateral extensor plantar responses. There was moderate neck stiffness. The cerebrospinal fluid was at 140 mm. pressure and was heavily blood-stained. Two hours later she suddenly collapsed, and became comatose. The cerebrospinal fluid pressure was 200 mm., and it contained an increase of blood.

Course.—She improved overnight but her breathing became stertorous and her chest "bubbly". The right arm then seemed more severely affected. Tone in all limbs was flaccid, with reduced tendon reflexes, the right more than the left. Both plantar responses were extensor. Bilateral carotid angiography showed gross atheromatous change, and possibly a small sac on the right internal carotid in the cavernous sinus. The left internal carotid artery was atheromatous in the same situation. Both anterior cerebral arteries were wide-swept, indicating the presence of internal hydrocephalus.

If anything, her level of consciousness lightened but in spite of antibiotic treatment she died of a chest infection on the third day of illness, before vertebral angiography had been carried out.

Necropsy.—The lateral ventricles (Fig. 3) were moderately dilated. The pons was very full with fresh blood over its surface and over the middle peduncles; the lateral recesses and cisterna magna were free from blood. The basilar artery was markedly atheromatous and showed a saccular aneurysm 5 mm. in diameter on the left side between the posterior cerebral and superior cerebellar arteries (Fig. 4). Section at the level of the mid pons showed an area of infarction on the right antero-lateral

aspect. On the left side there was a similar area of infarction on the lateral aspect. Blood was present in the fourth ventricle and there was haemorrhage into a small infarcted area in the postero-lateral part of the pons on the left side. On the right there was no involvement of the cerebellum, but on the left side there was an area of infarction anteriorly, and another posteriorly, with blood in the sulci. Lower down in the pons at the level of the nodule there was another extensive infarct on the right side (Fig. 2).

Infarction of the pons due to atheroma of the basilar artery was probably the important factor in this patient's respiratory infection and death, and it is doubtful whether immediate vertebral angiography would have affected the treatment.

Case 8.—G.S., a woman aged 34, developed severe headache and became unconscious. The cerebrospinal fluid was at a pressure of 200 mm., and heavily bloodstained. She recovered on the journey in the ambulance during transfer from the local hospital 12 hours after the haemorrhage.

Neurological Examination.—She was alert and cooperative. The right fundus was not seen due to haemorrhage, the left showed papilloedema. The tendon jerks were increased in the left limbs.

Course.—Bilateral carotid angiography was negative. Two days later the left eye became blind. A further haemorrhage occurred resulting in coma, inactive pupils, and twitching of the right arm. She recovered consciousness in 15 minutes, and showed a slight right facial palsy. Bilateral carotid angiography was again negative. She died on the sixth day after the haemorrhage.

At necropsy an aneurysm of the basilar artery was found situated between the anterior inferior and superior cerebellar arteries.

Case 9.—V.S., a woman aged 52, was found unconscious.

Neurological Examination.—Response to painful stimuli was just present. The pupils were fixed and unequal, the right larger than the left. There was a flaccid quadriplegia with absent jerks. The right plantar response was flexor, the left was equivocal. The cerebrospinal fluid was bloodstained.

Course.—Bilateral carotid angiography was normal.

Death occurred 10 hours after admission.

Necropsy.—A large aneurysm was situated at the midpart of the basilar artery with a large amount of clot extending to the foramen magnum.

Case 10.—R.R., a man aged 43, was heard by his wife to make a noise. She found him unconscious with his tongue protruding and his arms waving about. He recovered consciousness in half an hour, but was drowsy, irritable, and complained of frontal and occipital headache, and vomited.

Neurological Examination.—This showed neck rigidity and weakness of the right face and grip.

Course.—The cerebrospinal fluid was at a pressure of 300 mm., and bloodstained. After a further haemorrhage he developed bilateral papilloedema, weakness of the right leg, and bilateral extensor plantar responses.

Bilateral carotid angiography on two occasions showed no abnormality. A left vertebral artery suggested an aneurysmal dilatation at the bifurcation of the basilar artery, with a possible haematoma displacing the right superior cerebellar artery.

He died on the 26th day and at necropsy the haemorrhage was thought to be due to a small aneurysm at the junction of the right vertebral and basilar arteries.

Case 11.—E.J., a woman aged 68, had complained of headaches for seven years. She suddenly lost consciousness for 12 hours in one severe attack. On recovery she was drowsy, with occipital headache and neck stiffness.

Neurological Examination.—Three days later the patient was alert and cooperative but slightly confused. There were subhyaloid haemorrhages in the right fundus, the pupils were contracted and there were bilateral external rectus palsies. She had a right upper motor neurone facial weakness, and a left perceptive deafness. The blood pressure was 145/70 mm. Hg. There was massive albuminuria. The cerebrospinal fluid was uniformly bloodstained.

Course.—Bilateral carotid angiography and right vertebral angiography were negative. A left vertebral angiogram showed a small aneurysm of the left posterior inferior cerebellar artery. Three days later a right hemiparesis developed. Ventriculography was suggestive of a slight increase in the size of the ventricles. She ultimately made a good spontaneous recovery.

Case 12.—J.D., a man aged 62, suddenly developed weakness of the left leg, followed by severe frontal and occipital headache. He vomited on several occasions, but did not lose consciousness. The right leg then became affected.

He was treated at home for two days and power recovered in both legs, but he complained of headache and was drowsy.

Neurological Examination.—Neck rigidity was present. The ocular signs consisted of retinal haemorrhages, loss of the nasal field left eye, contracted pupils, and a left sixth nerve palsy. He moved the right limbs more readily than the left. Blood pressure was 200/140 mm. Hg. The heart was enlarged to the left. The cerebrospinal fluid pressure was 240 mm., and the fluid heavily bloodstained.

Course.—Bilateral carotid angiography was suggestive of a possible aneurysm on the left posterior communicating artery. His condition deteriorated, and on tapping blood was found in both ventricles. He died on the seventh day.

Necropsy.—The brain and brain-stem were oedematous, the latter on the right side. A large haemorrhage was found in the right cerebellar hemisphere due to an aneurysm of the right posterior inferior cerebellar artery.

We wish to thank Mr. Wylie McKissock for his kind permission to include Cases 8 to 12 from past records. We are also indebted to Dr. W. H. McMenemey for the pathological material from Case 7, and to the Photographic Department of the National Hospital for Figure 1.

REFERENCES

Atkinson, W. J. (1949). *J. Neurol. Neurosurg. Psychait.*, **12**, 137.
Bakay, L., and Sweet, W. H. (1953). *J. Neurosurg.*, **10**, 353.
Brain, W. Russell (1955). *Diseases of the Nervous System*, 5th ed. Oxford University Press, London.
Cairns, H. (1952). *Brain*, **75**, 109.
Dandy, W. E. (1944). *Intracranial Arterial Aneurysms*. Comstock Publishing Co., Ithaca, New York.
DeSaussure, R. L., Hunter, S. D., and Robertson, J. T. (1958). *J. Neurosurg.*, **15**, 385.
Elkington, J. St C. (1958). *Lancet*, **2**, 275.
French, L. A., and Haines, G. L. (1950). *J. Neurosurg.*, **7**, 156.
Kremer, M. (1958). *Brit. med. J.*, **2**, 121.
McDonald, C. A., and Korb, M. (1939). *Arch. Neurol. Psychiat. (Chicago)*, **42**, 298.
Norlén, G., and Barnum, A. S. (1953). *J. Neurosurg.*, **10**, 634.
Richardson, J. C., and Hyland, H. H. (1941). *Medicine (Baltimore)*, **20**, 1.
Rizzoli, H. V., and Hayes, G. J. (1953). *J. Neurosurg.*, **70**, 550.
Robertson, E. G. (1949). *Brain*, **72**, 150.
Schwartz, H. G. (1948). *J. Neurosurg.*, **5**, 312.
Spatz, E. L., and Bull, J. W. D. (1957). *Ibid.*, **14**, 543.
Taylor, A. B., and Whitfield, A. G. W. (1936). *Quart. J. Med. (n.s.)*, **5**, 461.
Tucker, J. S. (1958). *Electroenceph. clin. Neurophysiol.*, **10**, 405.
Uihlein, A., and Hughes, R. A. (1955). *Surg. Clin. N. Amer.*, **35**, 1071.
Walsh, L. S. (1957). *Results of Treatment of Spontaneous Subarachnoid Haemorrhage*. In *Modern Trends in Neurology*, Second Series, p. 119, ed. D. Williams. Butterworth, London.
Walton, J. N. (1956). *Subarachnoid Haemorrhage*. E. & S. Livingstone, Edinburgh and London.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 218.

THE ASSOCIATION OF CEREBRAL ANGIOMAS WITH INTRACRANIAL ANEURYSMS

BY

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The symptoms separately associated with both intracranial aneurysms and angiomas are well understood and their diagnosis now presents no special problem. Rarely the two lesions may coexist, sometimes with confused symptoms, or, when intracranial haemorrhage is the presenting symptom, with the precise source of haemorrhage in doubt. Walsh and King (1942) recorded the first case of an associated angioma and aneurysm, since when 13 further examples have appeared in the literature.

In this paper three new cases are reported and the previous literature reviewed; a distinction is made between a true arterial aneurysm coexisting with an angioma, and the aneurysmal sac which is part of the malformation itself. Cases in the latter category are excluded. Suggestions are made as to the nature of the association of the two lesions, and the clinical significance of their association described. Case 1, which presented with subarachnoid haemorrhage, is of special interest because arteriography clearly demonstrated which lesion had bled.

Case Reports

Case 1.—A married woman, aged 38, was admitted to the Hutt Hospital on September 6, 1957, under the care of Dr. R. Bakewell. Since the age of 12 she had had occasional left frontal headaches, usually on waking. On the morning of her admission she awoke with a headache which she took at first to be the usual migraine attack; on this occasion, however, the headache was occipital rather than above her left eye and her neck was stiff. The patient took some aspirin and left home to do some shopping; while waiting her turn to be served she suddenly lost consciousness.

On admission she complained of headache and neck stiffness but showed no localizing signs; lumbar puncture disclosed a heavily bloodstained fluid. Gradually headache became less severe and on the twelfth day bilateral carotid arteriography was performed. On the right side an aneurysm measuring 1·8 cm. in diameter was present on the pericallosal artery, the calibre of which, for 1 cm. proximal to the aneurysm, was reduced (Fig. 1a). The pericallosal artery was displaced 1 cm. to the left of the mid-line. In the left posterior parietal region an angioma was present, supplied by the left anterior and middle cerebral arteries (Fig. 1b).

The apparent spasm of the parent pericallosal vessel suggested that the source of haemorrhage was the aneurysm rather than the angioma; the patient was transferred to the Neurosurgical Unit, Dunedin Hospital, where at operation on September 26 a small intracerebral haemorrhage was found in the vicinity of the aneurysm

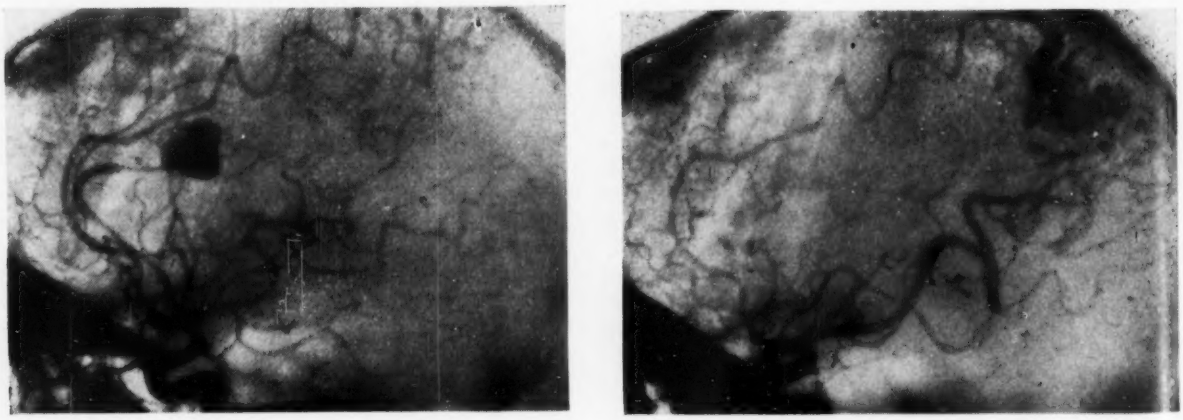

FIG. 1a and b.—Case 1: Bilateral carotid arteriograms showing an aneurysm 1·8 cm. in diameter on the right pericallosal artery and a medium-sized angioma in the left posterior parietal region. The calibre of the pericallosal artery for 1 cm. proximal to the aneurysm is markedly reduced.

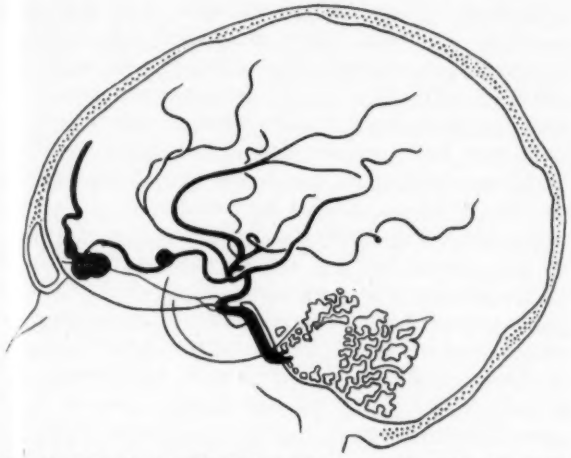

FIG. 2.—Case 2: A small angioma at the anterior extremity of the right frontal lobe with an arterial aneurysm on its feeding vessel.

FIG. 3.—Case 3: A large angioma in the right upper parietal region, fed by markedly dilated and tortuous middle cerebral vessels; from the internal carotid artery in the region of the posterior communicating artery, a small aneurysm projects downward and backward.

and in turn communicated with a subdural haematoma. Both left and right anterior cerebral arteries were clipped and the subdural haematoma evacuated.

Case 2.—A man of 49, a scrub-cutter, was at work when he suffered sudden bifrontal headache; he fell to his knees but did not lose consciousness. Almost immediately he noticed neck stiffness but after a short interval was able to walk the three miles out of the bush. He was admitted that day, November 26, 1951, to the Wanganui Hospital under the care of Dr. C. P. Powles.

On admission the diagnosis was established by finding heavily bloodstained fluid on lumbar puncture; there were no localizing signs. His headache gradually abated and he was free of symptoms when on December 13 he was transferred to the Palmerston North Hospital for further investigation. A right carotid arteriogram on December 20 showed an aneurysm, 7 mm. in diameter, on the fronto-polar branch of the right anterior cerebral artery; distal to the aneurysm the dilated fronto-polar artery continued to the anterior extremity of the frontal lobe to supply a small angioma (Fig. 2). Arteriography was not performed on the left side. The right common carotid artery was partially ligated on December 24 and ligation was completed three days later without incident. He was discharged home on December 31.

On February 19, 1952, the patient was admitted to the Neurosurgical Unit, Dunedin Hospital, and a right frontal craniotomy performed eight days later: the aneurysm was trapped and that part of the right frontal lobe containing the angioma excised.

Case 3.—A 49-year-old housewife was admitted to the Auckland Hospital under the care of Dr. E. G. Sayers on December 10, 1957, for the investigation of attacks of paraesthesiae and shaking in the left hand of 20 years' duration. Each attack began with a feeling of tingling in the left fingers, shortly followed by a twitching movement of flexion of the fingers and sometimes by blurring of vision; these symptoms lasted five to 10 minutes and for many years were followed by severe headache and vomiting. During the preceding two years she noticed a slowly progressive weakness and clumsiness of the left hand, although during this period the headache following each attack was less prominent. There was no family history of migraine.

On examination, a loud bruit was audible in both orbits and the right parietal region; apart from this the relevant physical findings were confined to the left arm. The left hand was noticeably smaller than the right, and there was a slight to moderate degree of generalized weakness of the extensor muscle groups and of the hand grip; the tendon reflexes in the left arm were brisker than those on the right side.

All laboratory investigations, including examination of the cerebrospinal fluid, were normal. An electroencephalogram showed a slightly asymmetrical voltage on the two sides with an otherwise normal background rhythm, the voltage on the right side being slightly less than that on the left.

No abnormality was present in the plain films of the skull. A right carotid arteriogram showed a large angioma in the right parietal region receiving its main blood supply from a markedly dilated middle cerebral artery; the internal carotid artery was also dilated. The anterior cerebral artery did not fill. At the junction of the internal carotid and posterior communicating arteries, a small aneurysm, measuring 3 mm. in diameter, was present (Fig. 3).

The patient was treated conservatively.

Review of Reported Cases

Thirteen case reports of a cerebral angioma associated with one or more intracranial aneurysms have been found in the literature. Some reports were necessarily brief and the clinical or pathological details incomplete; in these, further information

has been supplied by the original authors and is included in the following descriptions.

Walsh and King (1942) reported the first example of an associated aneurysm and angioma. Their patient, a Negro of 50, presented with intracranial haemorrhage. For four years previously he had suffered from intermittent right frontal headache and, from the first attack, a partial right third-nerve palsy. A clinical diagnosis of an aneurysm on the right side of the circle of Willis was made and at operation a large right supraclinoid aneurysm was found; it was, however, unruptured. The patient died several days later and at necropsy a left occipital angioma was revealed as the source of haemorrhage; a further small unruptured supraclinoid aneurysm was noted on the left side. Dandy (1944) later described the same case.

Arieti and Gray (1944) reported a further case, a man of 59 with a long history of epilepsy, disorderly behaviour, dypsomaniac attacks, and progressive mental deterioration. Necropsy revealed a left parietal angioma and a large left supraclinoid carotid aneurysm; in addition there were diffuse changes involving the subarachnoid vessels, similar to those in the angioma itself. Another aneurysm was present on the abdominal aorta.

Aring (1945) described the case of a woman of 30 who, when a child, began to have occasional minor fits and developed a left hemiparesis. She finally presented with multiple cranial nerve palsies and symptoms suggesting subarachnoid haemorrhage, dying four weeks after the onset. At necropsy an angioma occupied almost the whole of the right cerebral hemisphere; there were also unruptured aneurysms on the left posterior communicating, basilar, and anterior communicating arteries. Although on the fifth day the cerebrospinal fluid was grossly bloodstained, there was no evidence of intracranial haemorrhage post mortem. It may be presumed that the angioma was the source of haemorrhage.

Sugar (1951) successfully removed at operation both a large aneurysm and an angioma closely related to it but gave no details.

Laur (1953) reported in detail the history of a boy of 15 who initially presented with a right proptosis; a bruit was then audible over the whole of the left side of the skull. He shortly developed pulsating exophthalmos, frequent headache, and epilepsy. Arteriography disclosed a large left cerebral hemisphere angioma fed by an anomalous vertebral artery; on the right side a saccular aneurysm was present in the cavernous sinus, and two further aneurysms in the region of the anterior communicating artery also filled from this side. He was treated conservatively.

Hutton (1954) reported the next case, that of a man of 62, who, after a typical subarachnoid haemorrhage, was found on arteriography to have a left frontal angioma and an anterior communicating aneurysm which filled from the right side; the comment was made that in view of the impossibility of deciding which of the two lesions had bled, surgical treatment was considered inadvisable.

Walton (1956, 1958) described the case of a man of 48 who suffered a catastrophic subarachnoid haemorrhage. On admission to hospital within a few hours of the ictus he was deeply comatose with severe neck stiffness but no neurological signs; he deteriorated rapidly and died within 24 hours. At necropsy there was massive intraventricular and subarachnoid bleeding; a small angioma, 2 cm. in diameter, was found close to the wall of the posterior horn of the right lateral ventricle. There was also an unruptured aneurysm, 1 cm. in diameter, on the left posterior cerebral artery.

Paterson and McKissock (1956, 1958) described three cases. Their first was a man of 36 with a history of fits during the previous year; he showed no neurological signs. Arteriography demonstrated a large angioma at the left Sylvian point with multiple small aneurysms on the left anterior and middle cerebral arteries. He subsequently died from intracranial haemorrhage; no necropsy was performed.

Their second patient was a woman of 40 with a history of subarachnoid haemorrhage on three previous occasions. Arteriography disclosed a large right parietal angioma and two aneurysms on the dilated right internal carotid artery. She was treated conservatively and, three years later, remained well.

The third patient, a man of 54, died from a ruptured aneurysm found at necropsy to be situated on the right posterior inferior cerebellar artery 1·5 cm. from its origin; he also had had an episode of intracranial haemorrhage one year previously. An angioma was present in the left cerebellar hemisphere. Paterson (1957) described the same case.

Kremer (1957, 1958) reported two cases. The first was a woman, aged 48, with a history of episodic right-sided headache and left-sided sensory epileptic attacks since the age of 17; there was a further history of subarachnoid haemorrhage six weeks before admission. A loud bruit was heard over the scalp, especially to the right of the mid-line where there was a small cirsoid aneurysm, and a left homonymous hemianopic field defect was present with sensory impairment over the left side of the body. A right carotid arteriogram performed four years previously had revealed a large right parietal

angioma, and a left carotid arteriogram six weeks before admission had shown that the angioma extended across the mid-line. Following admission a vertebral arteriogram was performed and the angioma was seen to involve as well the territory of the right posterior cerebral artery. An aneurysm was present at the bifurcation of the basilar artery.

The second case was a man, aged 27, with a history of three generalized epileptic attacks at the age of 21 and two further attacks five years later. For two years he complained of left-sided headache and was finally admitted with a typical subarachnoid haemorrhage. Bilateral carotid arteriography showed an angioma at the left frontal pole fed by both internal carotid arteries, and an aneurysm on the anterior communicating artery which mainly filled from the right side. The angioma was successfully excised and the neck of the aneurysm clipped.

Brihaye and Blackwood (1957) made a detailed anatomical study of a large angioma in the right hemisphere of a man of 53 who, since early childhood, had suffered attacks of twitching of the left limbs sometimes followed by loss of consciousness. The diagnosis was finally established by arteriography following an episode of intracranial haemorrhage. At necropsy the angioma was seen to be fed mainly by dilated right anterior and middle cerebral arteries; on the supraclinoid portion of the right internal carotid artery, which was also dilated, were two small thin-walled saccular aneurysms. A further small aneurysm arose from the supraclinoid portion of the left internal carotid artery which was itself of normal calibre, and another aneurysm was present in the region of its bifurcation. On the posterior aspect of the basilar bifurcation two more aneurysms were present: it was one of these which had ruptured.

Discussion

What is the nature of this association of cerebral angiomas with intracranial aneurysms? If it be accepted that cerebral angiomas are congenital vascular malformations, and that intracranial aneurysms at least develop on the basis of a congenital vascular deficiency, then the association of the two lesions may be an expression of multiple disorders of vascular development. Under such circumstances patients with angiomas might be expected to show a higher incidence of aneurysms than an unselected sample of the population; this, however, does not appear to be the case. Of several large series of cerebral angiomas, only one, that of Paterson and McKissock (1956), described coexisting aneurysms; and in only three of their 110 patients with cerebral angiomas were aneurysms demonstrated. There are, nevertheless, two previously reported cases (Arieti and Gray, 1944; Laur, 1953) in which multiple congenital abnormalities were clearly present; Arieti and Gray used the term "progressive multiform angiosis" to describe the findings in their case which is, however, probably unique.

Paterson and McKissock (1956) suggested one further explanation of the association of the two lesions: that the increased blood flow consequent upon the presence of the angioma might throw abnormal stresses on the cerebral vessels concerned and so predispose to aneurysm formation. The prime haemodynamic effect of any arteriovenous shunt is to lower vascular resistance, and angiomas are no exception to this rule; according to Poiseuille's law the flow rate through the feeding vessel increases, often in practice to as much as three times the normal value. If there is any compensatory increase in cardiac output there will be a further increase in flow rate not only through the angioma itself but also through the whole of the brain; this increment amounted to approximately 30% in the two cases reported by Shenkin, Spitz, Grant, and Kety (1948). It is difficult to believe, however, that increased flow rate *per se* can predispose to the formation of saccular aneurysms: a more likely factor is the accompanying arterial dilatation, particularly if this is due to simple stretching, for this must aggravate any pre-existing congenital medial defect. Dible (1958) denied that such stretching is a factor of importance in the dilatation of an artery transmitting blood against lowered peripheral resistance; he suggested that the main factor is one of hyperplasia and hypertrophy involving the cells of the vessel wall. As all these changes, particularly the dilatation, are more pronounced on the side of the angioma, it might be expected that coexisting aneurysms would be commoner on that side; analysis of the present material does not, however, support this hypothesis. When the aneurysm is situated on the feeding vessel itself, as in Case 2, it is nevertheless difficult to believe that the altered haemodynamics have not in some way predisposed to its formation.

If the association of intracranial aneurysms with cerebral angiomas cannot be explained as an expression of multiple disorders of vascular development or on the basis of altered haemodynamics, the most likely explanation is that of coincidence. There have been various estimates of the frequency with which intracranial aneurysms are discovered in necropsy material, the most recent being that of Chason and Hindman (1958) who in a planned survey of 2,786 consecutive necropsies found 137 patients with congenital aneurysms, an incidence of 4·9%. This figure may be logically applied to patients with cerebral angiomas, almost 5% of whom should be found to harbour an intracranial aneurysm. That

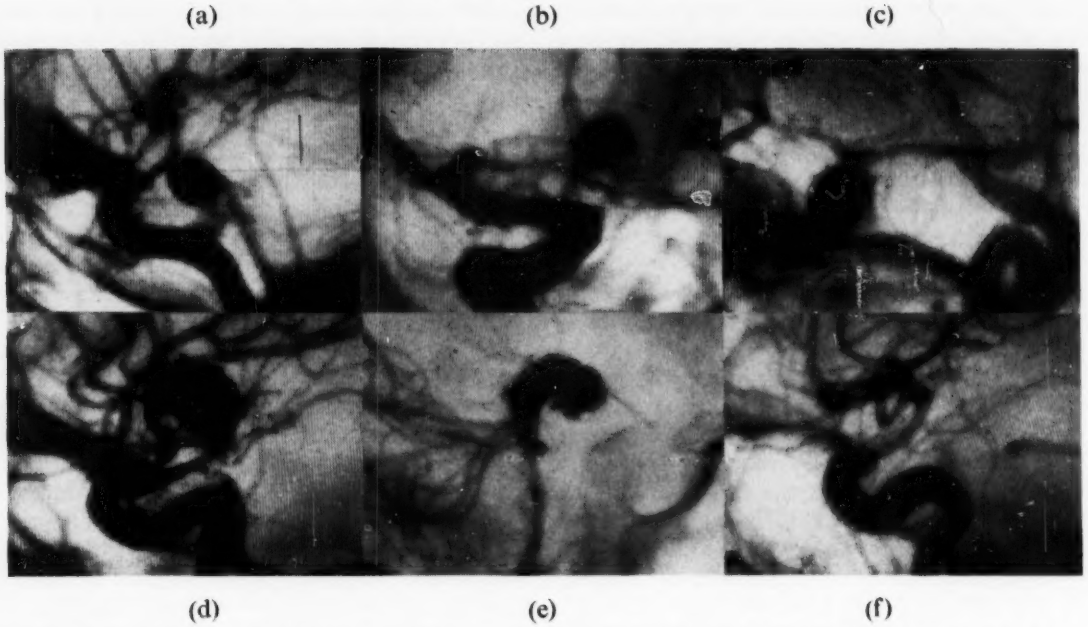

FIG. 4.—Typical examples of spasm involving the parent vessels of aneurysms in the following classical sites:—(a) Posterior communicating artery; (b) anterior communicating artery; (c) middle cerebral bifurcation; (d) internal carotid bifurcation; (e) basilar bifurcation; and (f) spasm of the internal carotid artery without any aneurysm demonstrated.

such an incidence has not been reported may be due to several factors. Thus, many supratentorial angiomas present with localizing signs and arteriography is then confined to the appropriate side; in few cases is vertebral arteriography as well as bilateral carotid arteriography performed. There are, moreover, certain inherent defects in the technique of cerebral arteriography whereby conventional antero-posterior and lateral views may fail to disclose very small aneurysms; this is probably a factor of some importance if the antero-posterior projection does not conform to certain standards (Boyd-Wilson, 1959).

The importance of the association of cerebral angiomas with intracranial aneurysms is twofold: the presence of both lesions may be responsible for confused symptoms, or, when intracranial haemorrhage is the presenting symptom, the precise source of haemorrhage may remain in doubt.

Analysis of the reported cases does not, however, suggest that confused symptoms are common; some such element is present in only three of the 15 cases in which a clinical history is available. There may be a history of a cranial nerve palsy due to the presence of the aneurysm, and the patient finally present with haemorrhage from the angioma, as in the case described by Walsh and King (1942); or there may be a history of epilepsy due to the angioma, and the patient present with haemorrhage from the aneurysm as in the case described by Brihaye and Blackwood (1957). In neither case would a correct clinical diagnosis be possible. More suggestive is the development of unexpected localizing signs as in Walsh and King's case, where, following a long history of right frontal headache and right third-nerve palsy due to the large supraclinoid aneurysm on the same side, the patient developed a right homonymous hemianopia: the basis for this, an angioma in the left occipital lobe, was revealed at necropsy.

If surgery is contemplated in those cases which present with intracranial haemorrhage it is of importance to determine which lesion is the source of haemorrhage, but in no previously reported case was this possible. Thus Hutton (1954), describing his case, considered an attempt at surgical treatment inadvisable in view of the difficulty in deciding which of the two lesions had bled. Of the three cases reported in this paper, the first is of interest because arteriography clearly demonstrated the source of haemorrhage. In this case a segment of the pericallosal artery proximal to the aneurysm showed the arteriographic appearance of spasm; it was presumed that the aneurysm, rather than the angioma, had bled and this was confirmed at operation. The occurrence of spasm in the region of recently ruptured intracranial aneurysms was well described by Ecker and Riemenschneider (1951) who, using the strict criterion of a return to normal calibre on subsequent arteriography, were able to show evidence of spasm in six out of a total of 29 cases of

urgically untreated subarachnoid haemorrhage. n their material the spasm was maximal at the site f the lesion and extended along the adjacent vessels or 1 cm. or more.

Of 46 aneurysms recently demonstrated by rteriography in the Wellington Hospital, 36 (in 25 atients) were associated with subarachnoid haemorhage; the calibre of the parent vessel of 16 of hese aneurysms (in 14 patients) was reduced (Fig. 4a to e). Of the remaining nine aneurysms nassociated with subarachnoid haemorrhage, there was no similar appearance of the parent vessel in any case. Of 14 cases of subarachnoid haemorrhage in which no aneurysm or other lesion was disclosed by meticulous arteriography, one showed constriction of the supraclinoid portion of one internal carotid artery (Fig. 4f), and another constriction of both internal carotid arteries as well as the basilar artery. In all cases of subarachnoid haemorrhage, arteriography was performed percutaneously using 42 to 48% "urografin", the great majority under local anaesthesia at the end of the first week.

Johnson, Potter, and Reid (1958) drew attention to certain pitfalls in the arteriographic diagnosis of spasm and suggested that the radiological appearances might on occasion have a different basis: thus, arterial constriction due to true spasm induced by traction on supporting arachnoid bands, in turn due to distension of the subarachnoid space by blood, might be maintained by damage to the vascular wall or by the pressure of blood clot. They described one case where "spasm" was present at operation and appeared unchanged in the post-mortem arteriogram. In the present series, one of the 14 patients with evidence of spasm came to necropsy two days after the arteriogram: all the affected vessels were then of normal calibre. In this case the arteriographic appearances were undoubtedly due to the presence of true spasm.

It may be said, then, that arterial constriction is commonly associated with arteriographically demonstrated intracranial aneurysms; that it is usually the parent vessel which is so affected, not vessels at a distance from the aneurysm; that more than one aneurysm in the same patient may be involved; that the appearances are associated with ruptured and not unruptured aneurysms; and, occasionally, that similar changes may be present in cases of subarachnoid haemorrhage when no aneurysm is demonstrated. Whatever the real nature of this constriction (probably due to true spasm in the majority of cases) the fact remains that such a finding constitutes valid evidence of recent haemorrhage, and is a radiological sign of importance when the source of haemorrhage remains in doubt.

Summary

Three new cases of associated cerebral angioma and intracranial aneurysm are reported, and the literature reviewed. Suggestions are made as to the nature of this association, the clinical significance of which is seen more particularly in cases which present with intracranial haemorrhage, the origin of which may be obscure. In one of the cases reported apparent spasm of the parent vessel suggested that the aneurysm, rather than the angioma, was the source of haemorrhage and this proved to be the case at operation. Such narrowing of the parent vessel is shown to be a radiological sign of importance when arteriography discloses more than one lesion as a possible source of haemorrhage.

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References

Arieti, S., and Gray, E. W. (1944). *Arch. Neurol. Psychiat.* (*Chicago*), **51**, 182.
Aring, C. D. (1945). *Dis. nerv. Syst.*, **6**, 119.
Boyd-Wilson, J. S. (1959). *J. Neurosurg.* **16**, 297.
Brihaye, J., and Blackwood, W. (1957). *J. Path. Bact.*, **73**, 25.
Chason, J. L., and Hindman, W. M. (1958). *Neurology*, **8**, 41.
Dandy, W. E. (1944). *Intracranial Arterial Aneurysms.* Comstock Publishing Co., Ithaca, New York.
Dible, J. H. (1958). *Lancet*, **1**, 1031.
Ecker, A., and Riemenschneider, P. A. (1951). *J. Neurosurg.*, **8**, 660.
Hutton, C. F. (1954). *Brit. J. Radiol.*, **27**, 471.
Johnson, R. J., Potter, J. M., and Reid, R. G. (1958). *J. Neurol. Neurosurg. Psychiat.*, **21**, 68.
Kremer, M. (1957). *Proc. roy. Soc. Med.*, **50**, 281.
—— (1958). Personal communication.
Laur, A. (1953). *Dtsch. Arch. klin. Med.*, **200**, 236.
Paterson, J. H. (1957). In *Modern Trends in Neurology* (second series), p. 105. Butterworth, London.
——, and McKissock, W. (1956). *Brain*, **79**, 233.
——, —— (1958). Personal communication.
Shenkin, H. A., Spitz., E. B., Grant, F. C., and Kety, S. S. (1948). *J. Neurosurg.*, **5**, 165.
Sugar, O. (1951). *Ibid.*, **8**, 3.
Walsh, F. B., and King, A. B. (1942). *Arch. Ophthal.* (*Chicago*), **27**, 1.
Walton, J. N. (1956). *Subarachnoid Haemorrhage.* Livingstone, Edinburgh and London.
—— (1958). Personal communication.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 224.

CONGENITAL ARTERIOVENOUS FISTULA WITH AN ANEURYSM OF THE GREAT CEREBRAL VEIN AND HYDROCEPHALUS TREATED SURGICALLY

BY

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Aneurysms occasionally develop from the great cerebral vein as a result of congenital arteriovenous fistulae. In a recent review Hirano and Terry (1958) referred to 18 cases, nine of which were confirmed at necropsy. The example of this rare condition reported here presented as a case of hydrocephalus showing certain noteworthy features. The condition responded well to surgical treatment, but the patient died after a fall. The connexions of the aneurysm were defined at necropsy.

Case Report

A baby girl of 6 months was brought for neurosurgical consultation because of obvious hydrocephalus in February, 1954. The pregnancy and delivery and the early development of the infant had been normal, and five weeks before she was examined she had been able to sit up almost unaided. At the time her balance had become impaired and she no longer raised her head spontaneously. The skull was seen to be expanded and superficial scalp veins were prominent. The skull circumference was 51·5 cm.; the fontanelle was half closed but tense. Eye movements and pupillary reactions were normal; no other abnormalities were detected. In radiographs of the skull, opening of sutures and finger markings of the vault were seen but there was no evidence of the cause of the increased pressure. The transverse sinuses were in their normal position and the posterior fossa was not unduly shallow. At ventriculography, the intracranial pressure was high and an obstruction of the aqueduct was demonstrated, but not with the flask-shaped outline usually found in aqueduct stenosis. The obstruction (Fig. 1) began 2 cm. below the third ventricle and increased caudally giving rise to a "rat tail" shadow. The aqueduct was displaced forwards and downwards suggesting a space-occupying lesion behind the pineal. To define this further, air was subsequently introduced by the lumbar route after the ventricular pressure had been lowered. The radiological appearances then were surprising (Fig. 2). All the subarachnoid cisterns were greatly dilated, particularly the cisterna ambiens. The sulci of the cerebral convexities were considerably enlarged up to the midline. These findings were interpreted to indicate defective absorption of fluid at the sagittal sinus as the primary cause of the hydrocephalus. It was thought that the resultant rise in fluid pressure in the subarachnoid space had caused dilatation of the cisterns to such a degree that the cisterna ambiens had obstructed the aqueduct and so produced a type of hydrocephalus which was at least intermittently non-communicating. To reverse this sequence an anastomosis between the spinal theca and the peritoneal cavity was made with polythene tubing on February 25, 1954. The immediate result was highly satisfactory: skull expansion ceased, the scalp veins became less distended, and normal development was resumed.

At the age of 1 year the child could stand with support; the skull circumference had increased by only 2 cm. At 18 months she could stand unaided; the fontanelles were closed. She had a normal vocabulary and the mother thought her intelligence was normal. At 2 years she could walk, but her vocabulary seemed a little behind her calendar age. At 3 years she appeared to be developing normally. The skull circumference was 56·5 cm. The

FIG. 1.—Ventriculography at 6 months of age. There is marked dilatation of the third ventricle and of the lateral ventricles (overlapping). The third ventricle is displaced upwards and forwards by the aneurysm. The aqueduct, initially dilated, tapers off distally. This unusual type of obstruction at the aqueduct has prevented air from entering the fourth ventricle.

FIG. 2.—Encephalogram after introduction of air into lumbar theca at 6 months of age. Radiotranslucent patches mark dilated subarachnoid cisterns and enlarge sulci over the cerebral convexity. This unusual picture indicates a failure of absorption of cerebrospinal fluid.

scalp veins were still prominent but they were not distended; abduction of the left eye was slightly impaired. At 4½ years old she could walk and talk adequately. Her gait was a little unsteady at times but there were no localizing signs of cerebellar dysfunction.

At 4 years and 8 months, in April, 1958, she fell while playing, striking and bruising the left frontal area. She quickly became drowsy and was admitted to hospital with a left hemiparesis and bilateral extensor plantar responses. A diagnosis of acute intracranial bleeding was made but bilateral exploratory burr holes did not reveal any haematoma; the brain was not under tension. During the next two days she became more alert and recovered the power of the left limbs. Forty-eight hours after admission, however, she became cyanosed and apnoeic, apparently as a result of acute ischaemia of the brain-stem, and she died within two hours.

Post-mortem Examination

Permission was granted for examination of the head only. The operation sites in the skull were in a satisfactory state. The skull was deformed but not markedly enlarged. The brain weighed 2,000 g. The convolutions were flattened and the brain tissue swollen. There was marked cerebral hydrocephalic deformity of the non-communicating type and the fourth ventricle was not enlarged; the lateral and medial apertures of the ventricle were patent. The subarachnoid cisterns were not enlarged. The brain was fixed entire together with the tentorium cerebelli, and subsequently sectioned in the coronal plane (Fig. 3). The ventricular system was obstructed at the aqueduct. The obstruction was caused by an external spherical swelling about 4 cm. in diameter with a fibrous wall. The swelling was an aneurysm extending downwards and forwards from the anterior end of the incisura tentorii and separating the brain-stem from the splenium. The antero-superior surface of this aneurysmal sac had stretched the posterior wall of the third ventricle, obliterated the recesses, and become firmly adherent to the pineal which was flattened antero-posteriorly. Hydrocephalic dilatation of the lateral ventricles and the upward and lateral pressure of the swelling into the calcarine fissures had thinned and flattened the medial surfaces of the occipital lobes so that the medial walls of the posterior horns of the lateral ventricles were stretched and attenuated. The usual deformities of cerebral hydrocephalus due to obstruction of the aqueduct were present, the cortex and white matter being reduced to a thickness of about 1·5 cm. in most places. The choroid plexuses were normal. The aneurysmal mass stretched the quadrigeminal plate below it to a thin membrane and the aqueduct was reduced to a transverse slit (Fig. 3). The superior vermis was compressed and formed the floor of a concavity which included also the medial parts of the lateral lobes of the cerebellum on either side. The fourth ventricle was slightly reduced in size.

There were no scars of the tentorium cerebelli or anything else to suggest previous tears and there was no evidence of haemorrhage from the aneurysm at any time. The aneurysm involved the posterior portion of the great cerebral vein and bulged downwards from the origin of the straight sinus at its origin at the apex of the tentorium. The straight

FIG. 3.—Coronal section through the aneurysm and the hydrocephalic brain at the level of the splenium, including the pons. A pale ball thrombus occupies part of the aneurysm. The aqueduct is patent but compressed below the aneurysm. The cerebral veins are dilated.

sinus was dilated to 1·3 cm. diameter and had a thick leathery wall. The torcula was an irregularly shaped cavity about 2·5 cm. wide. The right transverse sinus was also dilated (1·2 cm. wide) and thick walled. The left transverse sinus narrowed along its course and was 3 mm. wide at the point where the tentorium had been cut anteriorly. The superior sagittal sinus was 4 mm. wide. The aneurysm contained a white ball thrombus loosely adherent to its wall and not organized. The wall of the sac was about 1 mm. thick and microscopical examination showed that it was composed largely of elastic fibres and hyaline fibrous tissue formed in the intima of the vein. A similar intimal proliferation caused the thickening of the walls of the neighbouring venous sinuses.

On account of the stretching of the region, the vascular connexions of the aneurysm were identified with some difficulty and only after microscopical examination. It was possible, however, to locate and recognize the major veins and arteries and these are shown in Fig. 4. Angiomas were not found. The vessels were identified as follows.

Anteriorly both superficial middle cerebral veins were dilated and their entries into the cavernous sinuses were enlarged. Over the lateral surfaces of the hemispheres, the right vein was more dilated than the left. The right deep middle cerebral vein consisted of several small dilated vessels which drained into the basal vein. The right basal vein pursued an approximately normal course lateral to the cerebral peduncle and drained into the great cerebral vein where it was dilated into the aneurysm (Fig. 4). The left deep middle cerebral vein was dilated near its termination in the left basal vein on the cerebral peduncle. This left basal vein ended abnormally on the medial surface of the hemisphere behind the thalamus, external to the choroid plexus, and, together with the thalamo-striate and choroidal veins, gave origin to the left internal cerebral vein. The right internal cerebral vein was also identified by its origin in the thalamo-striate and choroidal veins on that side. Two-thirds of the way along its course it received an anomalous arterial tributary from the posterior cerebral artery, an arterio-venous fistula. The terminal third of the vein was dilated and varicose down to its termination in the great cerebral vein. The proximal 1 cm. of the great cerebral vein, between its origin in the union of the two internal cerebral veins and the aneurysm, was also dilated but not aneurysmal. On the right side it received a single small tributary from the posterior wall of the third ventricle. At the point of origin of the aneurysm the vein was joined by an arteriovenous fistula which was 2 mm. wide, a long arterial vessel which ran across the medial surface of the occipital lobe from the left posterior cerebral artery. The conjoined vessels entered the aneurysm at an angle, forming an opening 3 mm. wide in the lateral wall of the aneurysm. There were two other openings leading into the aneurysm, one of which was formed by the right basal vein and was 2 mm. wide. The inferior sagittal sinus, which was dilated, opened into the upper surface of the aneurysm close to the termination of the latter in the straight sinus. On microscopical examination, veins over the cerebrum, in the basal nuclei, and over the cervical portion of the spinal cord were seen to be dilated and their walls were fibrous. The arteries of the circle of Willis were normal.

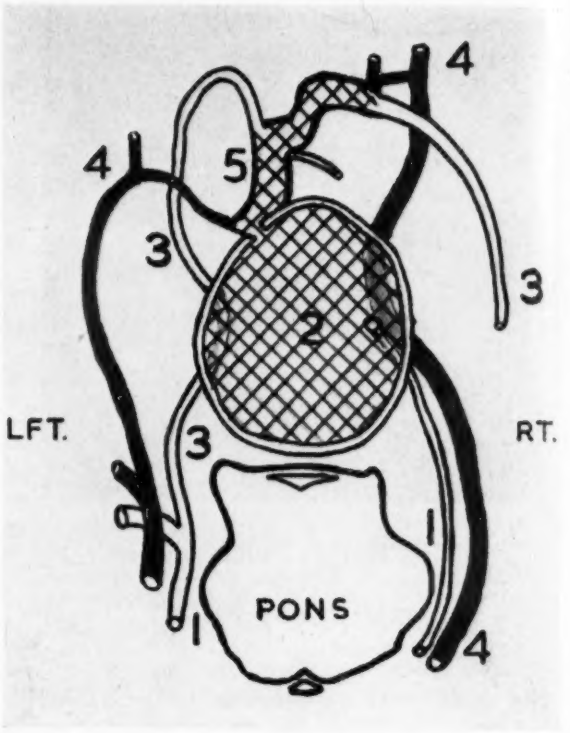

FIG. 4.—Semidiagrammatic representation of the aneurysm (2) at the distal end of the great cerebral vein and its vascular connexions. Branches of the posterior cerebral artery (4) are shown in black. The artery on the right lies in front of the aneurysm. There are arteriovenous fistulae, on the left to the dilated anterior portion of the great cerebral vein (5) where it enters the aneurysmal portion, and on the right to the terminal portion of the internal cerebral vein (3). Vessels containing mixed blood are cross-shaded. The right basal vein (1) ends in the aneurysm. The left basal vein (1) terminates abnormally at the origin of the left internal cerebral vein (3) which then passes in front of the aneurysm.

Discussion

Death resulted from the trauma sustained by the child while playing. Post-traumatic cerebral oedema was probably enhanced by the effects of the ball

thrombus in the aneurysm. Increased secretory activity on the part of the choroid plexus may have contributed to upset the delicate balance between production and absorption of cerebrospinal fluid which had been established by the previous thecoperitoneal drainage.

In the cases of Lumsden (1947) and of Clément, Gerbeaux, Combes-Hamelle, Pertuiset, and Pétranca, (1954, Case 1) the aneurysms were found in infants of 7 months and 1 month respectively and had caused subarachnoid haemorrhages. The ages of these cases and the location of the lesion might suggest that aneurysms of this type are caused by trauma at birth. In our case, however, there was nothing to indicate any previous tear of the tentorium and the existence of arteriovenous fistulae permits elimination of trauma as an aetiological factor with even greater certainty. Hirano and Terry (1958) have listed the arterial connexions of the aneurysms in the 18 cases in the literature. In 10 instances the posterior cerebral arteries were involved alone, as in our case, or in combination with other cerebral arteries. The anterior cerebral and pericallosal arteries were involved in other instances. Russell and Nevin (1940) reported the absence in their first case of any venous channels leading through the jugular foramina, and the terminations of the superficial middle cerebral veins in the cavernous sinuses were dilated. These terminations were dilated in our case too, but unfortunately the jugular foramina were not examined; the dilatation of the right transverse venous sinus suggests that drainage of blood was normal on that side, but in view of the narrowing of the other transverse sinus, the connexion of the left sigmoid sinus with the jugular vein may have been absent. Many of the deep and superficial cerebral veins on both sides were dilated and tortuous because of the increased entry of blood from the fistulae, but it was possible to identify all the major channels with normal anatomical elements. Thus, there was no genuinely angiomatous element in the anomaly and this seems to have been true also of the other cases which are discussed here, The extent of the venous anomalies described has varied considerably and may depend in part on the size of the arteriovenous fistulae. In the case of Jaeger and Forbes (1946), in which both arteries and veins were considerably enlarged, the fistula was big enough to lead to cardiac enlargement. The fistulae and the resultant aneurysm constitute a single entity, but it is to be expected that the lesion might occur from time to time in combination with arteriovenous malformations in other parts of the brain.

Superficial scalp veins are often dilated and prominent as in our case, because of their connexions with the cerebral venous system. Dilatation of superficial veins may be the presenting symptom (Boldrey and Miller, 1949). In the case of Hirano and Terry (1958) dilatation of venous channels caused protuberance of the right eye.

At necropsy, the walls of many of the cerebral veins were thick and fibrous, in keeping with the considerable degree of venous hypertension which certainly prevailed during life. The hypertension was probably the main factor impeding resorption of cerebrospinal fluid through the arachnoid granulations. In cases where subarachnoid haemorrhages have occurred, thickening of the leptomeninges may also interfere with resorption (Askenasy, Herzberger, and Wijsenbeek, 1953) but this complication was not present in our case. The dilatation of the subarachnoid cisterns noted before operation indicated that absorption of cerebrospinal fluid had been considerably impaired and this element of the hydrocephalus was relieved by thecal drainage. After operation the circumference of the head and the child's development began to approach normal. The cisterns were not dilated at death. The residual clinical signs were probably caused directly by the mass of the aneurysm. Possibly complete recession of the hydrocephalus was impossible at this time. In the case of Hirano and Terry (1958) the arterial feeders of the aneurysm closed spontaneously and completely but the hydrocephalus did not recede. Askenasy *et al.* (1953) suggest that deviation of arterial blood from the brain through the fistulae may increase the degree of cerebral atrophy caused by the elevation in cerebrospinal fluid pressure, but the clinical observations in our case do not support this suggestion. Although failure of absorption seems to have played the chief part in the genesis of the hydrocephalus, the direct effects of the aneurysm in compressing the aqueduct cannot be neglected, and the hydrocephalus may have been maintained to some extent by this means. The aqueduct was not completely closed, but obstruction may have been intermittent, as apparently in the case of Jaeger and Forbes (1946). The balance between production and absorption of cerebrospinal fluid achieved by the operation was a delicate one and was eventually upset by trauma.

Hydrocephalus was absent in a number of the cases reported in adults and older children (Oscherwitz and Davidoff, 1947; French and Peyton, 1954) but it has been the main symptom in children. The experience in the present case suggests that cerebrospinal fluid drainage operations have a useful part to play in its relief. Most often surgical treatment of the condition has taken the form of clipping the arterial feeders as fully as possible. Hirano and Terry (1958) point out that the chief value of such

operations probably lies in preventing subarachnoid haemorrhage and this complication has occurred often enough to deserve serious consideration. Personality changes have been recorded by French and Peyton (1954).

The presence of dilated superficial veins on the scalp in cases of hydrocephalus should arouse suspicion of the existence of an aneurysm of the great cerebral vein, and occasionally eye signs may suggest the presence of a lesion in the region of the pineal. In the present case there was slight abduction weakness of the left eye. Wolfe and France (1949) mention papilloedema and also evidence of defective innervation of the intrinsic and extrinsic muscles of the left eye. The patient of Jaeger and Forbes developed a squint while under observation. Eye signs were absent in the cases of Alpers and Forster (1945) and of Oscherwitz and Davidoff (1947). The diagnosis has most often been made by angiography but other radiological methods may be of use. The peculiar outline of the upper end of the aqueduct in the ventriculograms in our case may be paralleled in others. In several cases in adults the wall of the aneurysm has been partially calcified so that the dilated vessel was outlined (Alpers and Forster, 1945; Oscherwitz and Davidoff, 1947; Boldrey and Miller, 1949; Wolfe and France, 1949). The dilatation of the transverse sinuses might also in its turn lead to increased skull markings over the vessels, but the location of the sinuses on the skull is normal and they are not maintained in the foetal position as in congenital hydrocephalus due to atresia of the foramen of Magendie (Taggart and Walker, 1942; Gibson, 1955).

Summary

In a case of hydrocephalus caused by arteriovenous fistulae and an aneurysm of the posterior part of the great cerebral vein, the history and the necropsy findings in the head are recorded. Hydrocephalus and dilatation of superficial scalp veins were noted at 6 months of age. The hydrocephalus was found to be due in part to a failure of absorption of cerebrospinal fluid which probably resulted from high venous pressure in the superior sagittal sinus. A surgical spinal theco-peritoneal anastomosis was performed with good results. Since the operation compensated for the failure of absorption of cerebrospinal fluid by the natural routes, defective absorption appears to have played an important part in causing the hydrocephalus. The child died as the result of an accident when 4 years 8 months old. The aneurysm was found to have caused persistent but incomplete obstruction of the aqueduct. Associated vascular anomalies were marked dilatation of the anterior part of the great cerebral vein and of a portion of the right internal cerebral vein, arteriovenous fistulae on each side arising from branches of the posterior cerebral arteries, anomalous termination of the left basal vein, and elongation and dilatation of veins in many parts of the central nervous system. Angiomatous formations were not present. The case is discussed in relation to those reported by others.

We wish to thank Professor J. H. Biggart for advice and encouragement and Mr. D. McA. Mehaffey for the photographs.

References

Alpers, B. J., and Forster, F. M. (1945). *Arch. Neurol. Psychiat. (Chicago)*, **54**, 181.

Askenasy, H. M., Herzberger, E. E., and Wijsenbeek, H. S. (1953). *Neurology*, **3**, 213.

Boldrey, E., and Miller, E. R. (1949). *Arch. Neurol. Psychiat. (Chicago)*, **62**, 778.

Clément, R., Gerbeaux, J., Combes-Hamelle, A., Pertuiset, B., and Pétranca, C. (1954). *Presse méd.*, **62**, 658.

French, L. A., and Peyton, W. T. (1954). *J. Neurosurg.*, **11**, 488.

Gibson, J. B. (1955). *J. Neuropath. exp. Neurol.*, **14**, 244.

Hirano, A., and Terry, R. D. (1958). *Ibid.*, **17**, 424.

Jaeger, R., and Forbes, R. P. (1946). *Arch. Neurol. Psychiat. (Chicago)*, **55**, 591.

Lumsden, C. E. (1947). *J. Path. Bact.*, **59**, 328.

Oscherwitz, D., and Davidoff, L. M. (1947). *J. Neurosurg.*, **4**, 539.

Russell, D. S., and Nevin, S. (1940). *J. Path. Bact.*, **51**, 375.

Taggart, J. K., and Walker, A. E. (1942). *Arch. Neurol. Psychiat. (Chicago)*, **48**, 583.

Wolfe, H. R. I., and France, N. E. (1949). *Brit. J. Surg.*, **37**, 76.

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TRAUMATIC THROMBOSIS OF THE INTERNAL CAROTID ARTERY

BY

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Obstruction of the internal carotid artery by thrombus has been recognized with increasing frequency in recent years, because both carotid arteriography and inspection of this vessel post mortem have been done more often. Thrombosis following injury to the neck is well recognized and was described after both world wars, but in nearly all these cases there was laceration of the neck and an open wound in relation to the artery. But occasionally carotid thrombosis occurs after trauma which has not broken the skin of the neck, and it is with such cases of closed traumatic thrombosis of the internal carotid artery that this article is concerned. These have been regarded as rarities, and a rough idea of their frequency comes from Greco (1935) who recognized one such case whereas he saw 22 with open wounds, and from Caldwell and Hadden (1948) who described one case of carotid thrombosis due to closed trauma and eight with open wounds among some 25,000 wounded soldiers admitted to an American army hospital. Murray (1957) recently made a survey of the world literature and listed 10 cases from wounds of the neck, excluding cases such as Sedzimir (1955) described in which the thrombosis originated in the intracranial part of the internal carotid artery and was associated with a fracture of the skull base.

In addition to these analysed by Murray (1957), cases have been described by Cairns (1942), who also referred to another recognized by Zannoni (1933), by Sedzimir (1955) quoting an Australian case, and by Rosegay (1956) who describes one in America. Two further cases are now added, one recently seen in the Military Hospital, Wheatley, and the other associated with that hospital three years ago when the patient was sent to Oxford for rehabilitation after initial diagnosis at Cardiff.

Of these six cases, five survived, while in Murray's paper (1957) nine out of 10 died. The increasing use of arteriography makes it probable that many more such favourable cases will be recognized. The six patients who survived, one mentioned by Murray (1957) and five additional to his list, are briefly described.

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Case Reports

Case 1 (Schneider and Lemmen, 1952).—A 42-year-old woman sustained a fracture of the right clavicle with contusion of the right supraclavicular area in a car accident. She was normally conscious on arrival at the local hospital but was unable to move her left leg although the left arm was normal. She soon became lethargic and 12 hours later was semiconscious with a left hemiplegia and failure of conjugate eye movement to the left. Next day arteriography showed a block of the right internal carotid 3 cm. above its origin. Three months later she had a left hemiplegia, a left homonymous hemianopia, and was markedly labile emotionally.

Case 2 (Cairns, 1942).—A 23-year-old airman was knocked unconscious for perhaps three minutes in a crash landing. On arrival at hospital he could give a clear account of the accident but in a voice already so husky that, together with his difficulty in swallowing and breathing, a tracheotomy set was prepared although never used. There were superficial grazes in the left carotid triangle and a laceration, bleeding freely, on the right. However, it was on the former side that the damage occurred, for, about 30 hours later, despite apparent improvement, he suddenly became aphasic with paralysis of the right side of the face and of the right arm and with weakness of that leg. Craniotomy and air encephalography were both normal although six weeks later this latter investigation, on repetition, showed some dilatation of the left lateral ventricle. Thirty-eight days after the injury arteriography showed a block of the left internal carotid artery 2 cm. from its origin. One month later there was gross global dysphasia, a homonymous field defect in the right upper quadrant, right hemihypaesthesia, and some slight recovery of movement of the limbs on the right.

Case 3 (Sedzimir, 1955).—A 32-year-old man also improved over the year after his car accident so that he was then able to walk with an appliance although his left arm was useless. He had occasional grand mal attacks. His injuries had all been thought to be frontal and, again, loss of consciousness at the time of the accident was brief before he walked half a mile for help. Rational on entering hospital, he became unconscious

with the development of a left hemiplegia over a few hours during the next day. Angiography, on the basis of a diagnosis of subdural haematoma, showed a low complete obstruction of the right internal carotid.

Case 4 (Wheatley Hospital No. N 2092).—A 20-year-old soldier was knocked out in a dance-hall brawl. There were small cuts on the lower lip and the left side of the chin while there was also slight swelling of the left side of the neck, although it never felt stiff. He was unconscious on admission to hospital and did not regain consciousness for some 12 hours when he was unable to speak or to write. He also had a marked right facial palsy and some weakness of the right hand, but not to a degree that could explain the agraphia. This hand and his writing showed most improvement so that, although he began to say words 10 days after the injury, 10 weeks after the accident there was still considerable dysphasia, but no nominal dysphasia or apparent defect of internal speech, together with a right facial weakness. Six weeks after the accident the fields were normal. Arteriography at this time showed a proximal obstruction of the left internal carotid.

The last two cases both show carotid obstruction distally, recalling the cases of Sedzimir (1955) but without any evidence of skull fracture such as he found.

Case 5 (Rosegay, 1956).—A 29-year-old man was knocked out in a fight but soon came round to notice weakness and numbness of the left arm and leg which progressed so that next day there was a severe left spastic hemiparesis. At a stage when recovery had already begun in the leg, arteriography showed a block of the right internal carotid artery just distal to the origin of the posterior communicating artery. The leg continued to improve but the hand remained virtually without function. This case again showed no delay between the trauma and the onset of neurological deficit.

Case 6 (Wheatley Hospital No. A 25187).—A 21-year-old professional boxer lost a fight on points but did not receive particularly severe punishment or any noticeable injury to his neck. About three-quarters of an hour later, he vomited and then rapidly developed motor aphasia and a right hemiparesis. He came under the care of Mr. C. Langmaid, at Cardiff, and arteriography showed the obstruction again to be high in the left internal carotid, at the base of the skull. Recovery in the right leg and in speech had begun 10 days after the fight while six weeks later, when he came to Oxford for rehabilitation, there was only mild nominal dysphasia, slow speech, a moderate right facial weakness, severe spastic paralysis of the arm, a moderate spastic paresis of the leg (but not severe enough to need a toe-spring), and a mild left hemianaesthesia, but no visual loss. Three years later, he is completely independent but there is still almost complete lack of movement in the right forearm and hand. Interestingly, in view of the transitory aphasia, he is a left-handed man with a history of left-handedness in the family.

Discussion

These six surviving cases may be grouped with the other cases of closed traumatic thrombosis of the internal carotid artery listed by Murray (1957) or mentioned earlier in the paper (Zannoni, 1933), so that there are 16 cases for discussion.

The youngest patient was 16 and the oldest 45 years of age, while 10 were aged 20 to 30 years. This age group is probably more liable to trauma than are others, but the incidence is nevertheless remarkably high. As might be expected on similar grounds, males form the bulk of the patients.

The initial injury is not usually severe and later examination shows only some abrasions of the face or neck, contusion or mild swelling of the neck, or, occasionally, a fracture of the jaw, clavicle, or first rib (in one instance each). The cause may be an accident while travelling, a blow in a fight or from a flying missile, or, in one bizarre case (Northcroft and Morgan, 1944) the embrace of a rope which trailed from a passing lorry to wrap itself round a pedestrian's neck, throw him to the ground, and then unwind again. This initial injury might cause unconsciousness for a few minutes but in most cases the patient was regarded at first as having sustained only minor injuries, and, indeed, might walk some distance to a hospital for an abrasion to be dressed, or merely go straight home. The onset of symptoms is most commonly in the first six hours but may occur some 30 hours after the accident, as shown in Table I.

TABLE I

ONSET OF SYMPTOMS AFTER ACCIDENT

Time after accident (hr.)	Immediate	0–6	6–12	12–24	24–36
Number of cases	2	6	3	3	2

Two cases were unusual, for one patient (Case 4) was unconscious for 12 hours after the accident when he recovered with signs of left cerebral dysfunction while the other (Case 5) had weakness and numbness of the left arm immediately he recovered from a few minutes of unconsciousness. Clarke and Harris (1958) write that an interval between the trauma and the development of altered consciousness is a constant feature of traumatic carotid thrombosis. In Case 4 the 12 hours of unconsciousness may have resulted from a cause other than the blockage of an internal carotid artery, which lesion could have developed during that period to be responsible at its end for aphasia, agraphia, and palsy of the right face and hand. And in Case 5, it was malfunction of the left arm that was present and progressive, for there was no period of disturbed consciousness apart from a few minutes immediately after the accident. Both these patients survived.

There seem two possible sites of obstruction. Of 0 cases with adequate necropsy reports, nine showed amage to the intima and usually the media of the rtery in the 2 to 3 cm. above the bifurcation of the ommon carotid with corresponding thrombus formation, while in one extravasation of blood into he carotid sheath at this level was the most prominent feature apart from the thrombus itself. n the six survivors, where there is only arteriographic evidence, the block was near the origin of the internal carotid in four and high in its course in two, where it was described respectively as at the base of the skull (Case 6) and just distal to the origin of the posterior communicating artery (Case 5).

Obstruction low in the internal carotid does not itself indicate where the thrombus originated, for spread may be retrograde, but, as just mentioned, in nearly all the necropsy cases there was clearly intimal damage near the proximal end of the clot. Indeed, distal spread is the rule for, of 10 cases, spread to the beginning of the middle cerebral artery had occurred in nine while in five of them the anterior cerebral artery was also involved. Occasionally thrombus was also seen in the posterior cerebral or even basilar artery. The effect upon cerebral nourishment of the spread of a thrombus to break the continuity of the circle of Willis and perhaps extend along a cerebral artery must be considerable. If extension blocks the middle cerebral artery alone the anterior cerebral artery could still be fed from the opposite side. Of 16 cases considered, motor involvement of the arm and leg seemed equally severe in 10, in two the leg was worse than the arm, and in four the arm was the worse. Not surprisingly, of these six patients with more partial lesions, five were survivors so that clinical and post-mortem findings cannot be compared. In the one exception (Clarke, Dickson, and Smith, 1955), where the arm was affected almost 24 hours before the leg, the thrombus was found at necropsy to extend to the origin of the middle and anterior cerebral arteries. Sedzimir (1955) describes an interesting case where thrombotic obstruction of the internal carotid artery, originating from the region where it passes upwards from the cavernous sinus, and associated with rhinorrhoea and a fracture of the cribriform plate, caused paresis of the right arm several hours before coma occurred and some days before the leg was paralysed. Here again the thrombus extended only to the point of bifurcation of the internal carotid artery.

The survivors show no special features to distinguish them from those who died, either in the nature of the accident, the severity of apparent damage at an early stage, or the time before neurological symptoms appeared. They do include one case (Cairns, 1942) where a cerebral deficit appeared suddenly and as late as 30 hours after the original injury. Cairns felt that distal embolism from a carotid clot accounted for the sudden onset in this young pilot of hemiplegia and aphasia and supported this view by reference to the case described by Zannoni (1933) where at necropsy there was a slightly adherent clot in the middle cerebral artery not in continuity with clot firmly adherent at the proximal end of the internal carotid artery.

The severity of the residual damage in these cases varies from a right facial weakness with a dysphasia not severe enough to prevent the patient from conveying his meaning (Case 4) to a man with dysphasia, hemiplegia, hemihypaesthesia, and an upper quadrantic homonymous field defect (Case 2). In only one of the six were grand mal attacks a sequel (Case 3).

The cases presented here may be contrasted with two described by Sedzimir (1955) in which the distal end of the internal carotid artery was occluded after trauma, which also caused fracture of the cribriform plate on one side and rhinorrhoea. In these two patients, aged 54 and 42, respectively, there was a long period of unconsciousness immediately following the injury (five days and continuous to death). The onset of focal signs came relatively late, on the seventh day in the first case and after two days in the other. Both these patients died. The rare cases in which injury occurs through the soft palate (Fairburn, 1957) have not been considered here.

Summary

Two further cases of thrombosis of the internal carotid artery after non-penetrating injury are described. They both survived and are grouped with four other surviving cases to contrast with a recent list in which nine out of 10 died. Some features of the lesion are discussed.

I wish to thank Dr. W. Ritchie Russell for his help in the preparation of this paper, and the Director of the Royal Army Medical Corps for permission to publish it.

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References

Cairns, H. (1942). *Lisboa med.*, **19**, 375.
Caldwell, H. W., and Hadden, F. C. (1948). *Ann. intern. Med.*, **28**, 1132.
Clarke, E., and Harris, P. (1958). *Lancet*, **1**, 1085.
Clarke, P. R. R., Dickson, J., and Smith, B. J. (1955). *Brit. J. Surg.*, **43**, 215.
Fairburn, B. (1957). *Brit. med. J.*, **2**, 750.
Greco, T. (1935). *Arch. ital. Chir.*, **39**, 757.
Murray, D. S. (1957). *Brit. J. Surg.*, **44**, 556.
Northcroft, G. B., and Morgan, A. D. (1944). *Ibid.*, **32**, 105.
Rosegay, H. (1956). *Neurology*, **6**, 143.
Schneider, R. C., and Lemmen, L. J. (1952). *J. Neurosurg.*, **9**, 495.
Sedzimir, C. B. (1955). *J. Neurol. Neurosurg. Psychiat.*, **18**, 293.
Zannoni (1933). Cited by Cairns (see above).

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 232.

CLINICAL AND ELECTROENCEPHALOGRAPHIC INVESTIGATIONS IN MYOCLONIC CEREBELLAR DYSSYNERGIA

BY

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Clinical and anatomical evidence hitherto published on Ramsay Hunt's (1921) myoclonic cerebellar dyssynergia has not succeeded in establishing the nosological place of this clinical entity, which van Bogaert considers to be a cerebellar syndrome with a superimposed myoclonic epilepsy. However, the clinical and electroencephalographic evidence does not permit such a conclusion. The case published by Cristophe and Rémond (1951), followed later by an anatomical study (Christophe and Gruner, 1956), presented cerebellar manifestations associated with typical electroclinical myoclonus, synchronous and symmetrical discharges of spike-and-wave and polyspike-and-wave complexes, and of myoclonus activated by intermittent photic stimulation, whereas the cases reported by Alajouanine, Scherrer, Contamin, Marteau, and Calvet (1955), Daum, Lecasble, and Foncin (1953), and De Risio (1957 had no electroencephalographic accompaniments to the myoclonic discharge. The case reported by Daum and others (1953) did not even display a cerebellar syndrome 17 years after the onset of the disease. The disease sometimes follows a prolonged monosymptomatic course, irrespective of its having begun with cerebellar manifestations or with myoclonus. The E.E.G. and clinical evidence reported in the present paper is a contribution to its pathogenesis and nosological classification.

Case Reports

We examined clinically and electroencephalographically a girl displaying the typical syndrome, which was also seen in her parents and two brothers, aged 12 and 7 years respectively.

In the case of Elisa P., aged 15 years, no occupation, the disease appeared at the age of 11, with a nocturnal generalized convulsive seizure. She had similar convulsive seizures during the following nights. Four weeks after the onset of the disease it was noticed that during the day-time the patient displayed sudden jerks, which made her fall. These jerks were followed by a discharge of generalized myoclonus (involving the limbs and face), associated sometimes with, sometimes without, displacement of the limb segment. Despite the patient's statement that such seizures during the day were associated with loss of consciousness those who witnessed them stated that the patient spoke in a broken voice and asked not to be assisted as she was able to get up by herself. It may be assumed either that she did not wholly lose consciousness or that its loss was but transitory. These seizures were more frequent in the morning, particularly when the patient got out of bed, and in the evening. They occurred about five or six times every day. At the same time the patient noticed the onset of a tremor and small muscular jerks which interfered with each movement of the hands. She became clumsy and dropped things. Her voice was broken. Jerks were likewise present in the muscles of the face and distal extremity of the limbs, with or without segmental displacement; they were in no way related to falls, but emotional upset and even the smallest voluntary act aggravated them. For the past three years she had had no more generalized seizures, but the myoclonic manifestations had become more intense. It was also noticed that her legs suddenly gave way during walking, thereby making her fall.

On neurological examination, the patient stood upright on a wide base, and she could walk also on a wide base. It was noticed that one of the knees, either the right or the left, suddenly gave way involuntarily from time to time; muscular jerks and oscillations of the trunk were also present. Active movement was possible in all limb segments, but it was interfered with by muscular jerks affecting mainly the distal extremities of the limbs. There was hypotonia in the lower limbs. The ankle jerks were abolished. The plantar cutaneous reflex was normal; the right upper abdominal reflex was the only one left unimpaired but it was rapidly exhausted. There was normal sensibility, both superficial and deep. The patient exhibited the following cerebellar signs: intention tremor in the forefinger-nose test, bilateral adiadokokinesis, with the arms stretched forward there was a rapid tremor of the fingers with a small amplitude, dysmetria and hypermetria were elicited by all the tests, asynergia of the trunk in Babinski's overturning test, bilateral Stewart Holmes reaction. Speech was broken and somewhat explosive. Writing was macrographic, with an irregular, quavering touch, so that some strokes were invisible due to a jerk displacing the whole limb.

When lying the patient displayed no tremor and the muscular jerks were very infrequent. In the upright

osition they affected all the muscle groups, including ne face in the form of fasciculations. The myoclonus as irregular, asymmetrical and it was exaggerated by xertion and emotion. Sudden jerks of the muscles of the unk, making the patient fall, followed by myoclonic ischarges lasting three or four minutes, without loss of onsciousness, were noticed. There was nystagmus on ateral gaze.

Psychiatric examination disclosed puerilism and slight behaviour disorder.

Laboratory examinations were normal, apart from a mild normochromic anaemia. The cerebrospinal fluid was normal.

Air encephalography revealed slight enlargement of the third ventricle and of the aqueduct of Sylvius. Air was present in the major cistern as well as in the prepeduncular cistern.

Electroencephalographic examination showed a rather polymorphous background tracing (Fig. 1); it consisted of a rapid rhythm of 14 c./sec. and of waves in the theta band at the rate of 5 c./sec., either isolated or in outbursts, and had the appearance of positive sharp waves with a bilateral temporo-central and temporo-occipital location. They sometimes formed paroxysmal discharges with a low frequency, lasting between four and 10 seconds, without the patient losing consciousness. The generalized paroxysm was characterized by another type of discharge, which was very frequent and brief (one to two sec.) occurring at regular intervals and characterized by generalized outbursts of spike-and-wave, polyspike-and-wave, or sinusoidal waves with a frequency of 5 c./sec. (Fig. 1). These discharges were not activated by the intermittent light stimulation and they did not correspond with the myoclonus. During these discharges she answered correctly a question asked in advance and the answer she gave afterwards to a question asked during the discharge was equally correct. When asked a question, she developed myoclonus in the facial muscles before answering, which caused deterioration in the electroencephalographic tracing. The records displayed a close relationship between the facial myoclonus and the answers, but, on the other hand, there was no visible relationship between the discharges and the myoclonus. Myoclonus and fasciculation occurring in other muscle groups displayed the same characteristics (Fig. 3).

Hyperpnoea brought about a slow dysrhythmia in all leads but chiefly in anterior leads.

Largactil (75 mg. daily) brought about an obvious clinical improvement. The myoclonus and fasciculation became less frequent and troublesome. The background activity was irregular, there was a greater number of waves in the theta band, positive sharp waves both isolated and in outbursts, rapid rhythms of 20 c./sec., mainly in anterior leads. Though irregular, the generalized paroxysm of spike-and-waves and polyspike-and-waves had a somewhat higher frequency (6 per sec.) (Fig. 2). An intramuscular injection of 0·25 mg. adrenaline, administered under the effect of "largactil", did not in any way change the electroencephalographic pattern. An intramuscular injection of 0·2 g. acetylcholine, given under similar conditions, improved the background activity: the positive sharp waves were less numerous and the outbursts were less prolonged, their amplitude was smaller. The generalized discharges (characterized by hypersynchronous waves) had a frequency of four or five per minute and were shorter.

Six days after "largactil" therapy had been discontinued, the electroencephalographic tracing resumed its initial pattern. The positive sharp waves were in greater numbers and in particular the outbursts were more prolonged, displaying a left centro-occipital predominance.

Adrenaline, 0·5 mg., given intramuscularly caused no electrocardiographic or electroencephalographic change. Clinically, the myoclonus became more frequent and more generalized. The electroencephalographic and clinical picture remained unchanged after an injection of neoeserin. An injection of 4 mg. strychnine did not modify the pattern of the tracings, but the myoclonus became more ample and frequent, particularly when the patient answered questions (Fig. 3).

Delayed mental development of Emmanuel P., aged 12 years, a brother of Elisa P., had been noticed since early childhood. He did not recognize persons around him until he was 4 years of age. He learned the names of objects at the age of 5. He could not attend school because he was unable to learn or concentrate or observe school discipline. He could learn no trade, nor could he perform any consequent activity. He displayed seizures of psychomotor agitation which sometimes attained great violence.

There was nothing worth mentioning in the child's past history.

A neurological examination was negative.

Psychiatric examination showed a second degree oligophrenia.

Electroencephalographic examination showed light-reactive background activity displaying waves in the alpha band, at the rate of 10 c./sec., waves in the theta band at the rate of 4 c./sec., particularly in anterior leads. The tracing was rather poorly organized for the child's age. Discharges lasting one or two seconds were noticed to appear against this background, characterized by atypical spike-and-wave complexes at the rate of 4 c./sec., slow biphasic spikes or hypersynchronous biphasic waves attaining the greatest amplitude in the left temporo central lead (Fig. 4). The discharges were not accompanied by any myoclonic manifestations. Hyperpnoea exerted no influence.

Thirty minutes after the ingestion of 50 mg. "largactil", the child was drowsy. Fifteen minutes later, he became clumsy in the performance of voluntary actions. Each movement was interfered with by myoclonus, similar to that displayed by his sister. The electroencephalographic tracings exhibited marked alterations. Biphasic spikes or even slow isolated spike-and-waves were noticed, chiefly in central leads. Spike-and-wave discharges were more frequent and persistent (Fig. 5). Paroxysmal dysrhythmic periods were noticed in the central region lasting 20 to 27 seconds, characterized by slow waves, positive sharp waves, positive spikes with an inconstant frequency. Phase reversal could be elicited between the central electrodes (Fig. 6).

After a subcutaneous injection of adrenaline (0·5 mg.)

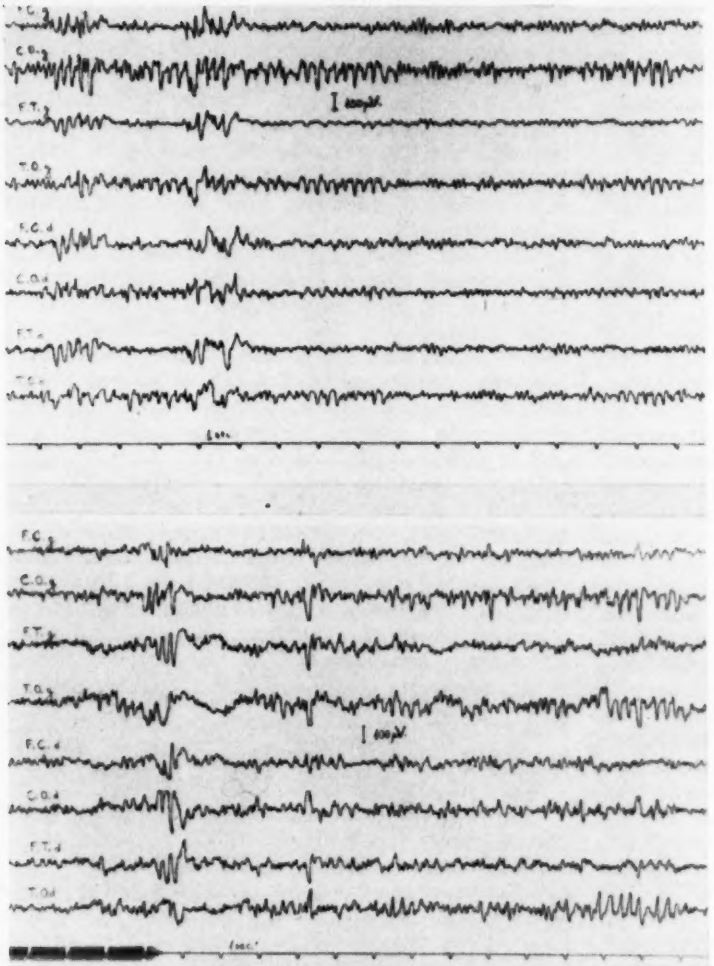

FIG. 1.—*Elisa P.* Polymorphous background tracings: rapid rhythm at the rate of 14 c./sec., waves in the band at the rate of 5 c./sec., either isolated or in outbursts. Paroxysmal outbursts of positive sharp waves with a bilateral temporo-central and temporo-occipital location, lasting four to 10 seconds. Brief discharges of generalized outbursts, spike-and-waves, polyspike-and-waves, or sinusoidal waves with a frequency of 5 c./sec.

FIG. 2.—*Elisa P.* Largactil (75 mg. daily) causes greater alteration in the tracing: a more irregular background activity, a greater number of theta waves, sharp waves, and rapid rhythms of 20 c./sec. in anterior leads.

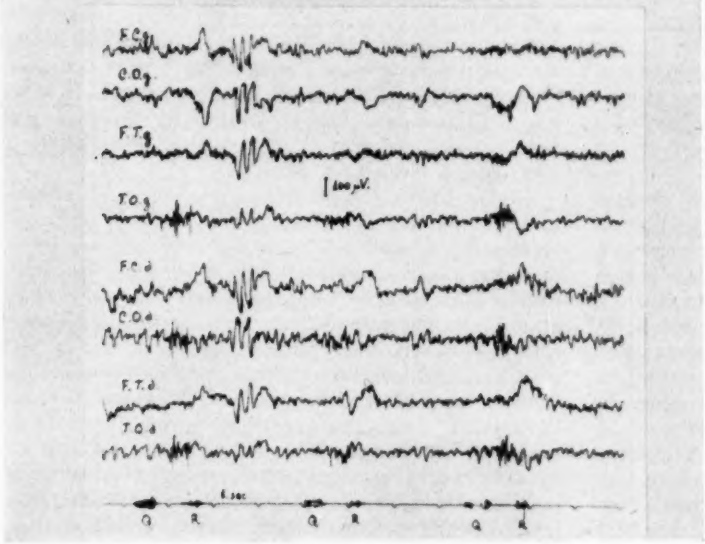

FIG. 3.—An injection of 4 mg. strychnine does not alter the appearance of the tracings, but myoclonus is more ample and more frequent, chiefly when the patient answers questions.

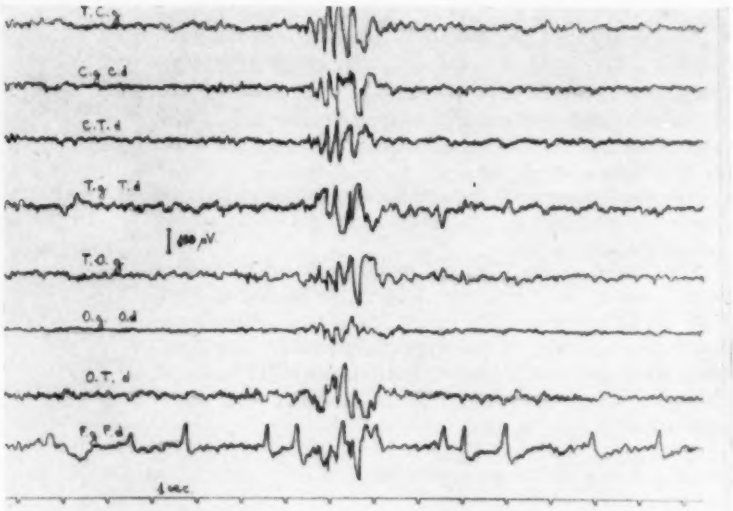

FIG. 4.—*Emmanuel P.* A poorly organized electroencephalographic tracing for his age. Discharges lasting one or two seconds of atypical spike-and-waves complexes at the rate of 4 c./sec., attaining the greatest amplitude in the left temporo-central derivation.

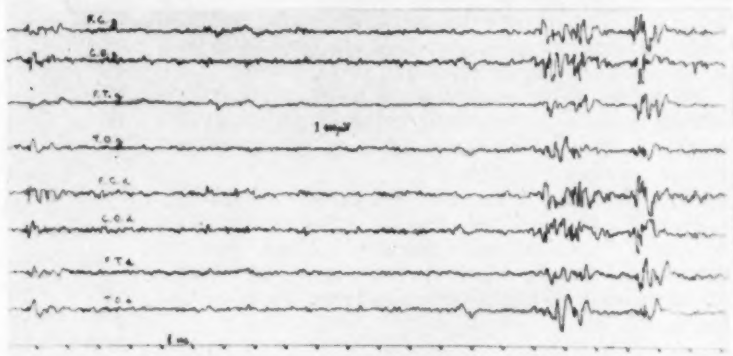

FIG. 5.—*Emmanuel P.* Thirty minutes after the ingestion of 50 mg. "largactil" the tracings exhibit marked alterations. Biphasic spikes, or even slow isolated spike-and-waves are seen. Spike-and-wave discharges are more frequent and persistent.

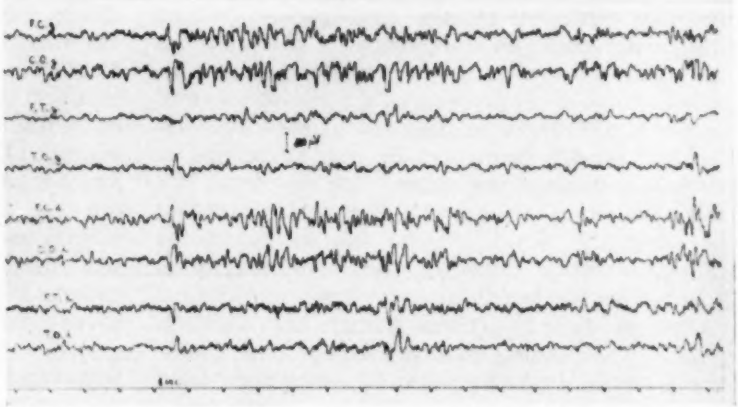

FIG. 6.—*Emmanuel P.* Same situation as in the former figure. Paroxysmal dysrhythmia appears in the central region, lasting 20 to 22 seconds, characterized by slow, positive, sharp waves and positive spikes. Phase reversal can be noticed between the central electrodes.

the tracings displayed a score of sharp waves, isolated and grouped, slow biphasic spikes, waves in the theta band at the rate of 4 c./sec. No generalized discharge of spike-and-waves was visible any more.

Florian P., aged 7 years, was the third child. He displayed somewhat marked mental retardation.

Neurological examination elicited an oscillating gait and dysmetria and intention tremor, chiefly in the limbs on the right side.

Air encephalography showed a slight degree of internal hydrocephalus and a considerable amount of air in the prepeduncular cistern.

The electroencephalogram revealed normal tracings with sparse bi- and triphasic spikes in the central regions. The background activity in posterior leads was somewhat slow (8 c./sec.). Hyperpnoea gave rise to ample, sinusoidal, symmetrical, generalized waves, within normal limits for the patient's age. Intermittent light stimulation did not alter the tracing.

A dose of 50 mg. "largactil" did not modify the tracings but a discharge resembling the ones elicited in his sister was noticed.

Marin P., the children's father, aged 47 years, a laboratory assistant, exhibited no subjective disorder. His father (the children's grandfather), who died with psychiatric disorders when aged 75 years, had had syphilis. No case of epilepsy or other neurological diseases was noted in the father's family.

Neurological examination showed loss of the tendon reflexes in the lower limbs and diminution of the tendon reflexes in the upper limbs. Gyratory nystagmus was present on right lateral gaze.

The electroencephalographic tracings were normal.

Zinca P., the children's mother, aged 45 years, no occupation, was mentally deficient. There were no neurological factors worth mentioning in her family. The electroencephalographic tracings were within normal limits.

Discussion

The clinical picture, the course of the disease, and the alterations in electroencephalographic tracings exhibited by the first patient suggest myoclonic cerebellar dyssynergia. The onset is somewhat unusual as the first manifestations consisted of nocturnal generalized convulsive seizures. In her two brothers the diagnosis is more difficult. In the case of Emmanuel P., the alterations in electroencephalographic tracings are very much like those found in his sister. The untoward effect of "largactil", which, in the case of Emmanuel caused cerebellar disorders and myoclonia, is in contrast to the beneficial effect upon the clinical symptoms elicited in Elisa, though both children displayed the same electroencephalographic alterations, chiefly an aggravation of centralencephalic discharges with a temporal projection, which sometimes have the actual appearance of seizures of temporal epilepsy lacking any clinical manifestation. We believe that Emmanuel is likewise a case of Ramsay Hunt's disease, though at an earlier stage, before the onset of clinical cerebellar or myoclonic manifestations. The mild cerebellar disorders displayed by the youngest child, Florian, and by their father are more difficult to interpret. The very slight electroencephalographic disorders elicited in the case of Florian and the absence of any alteration in the father in no way rule out the diagnosis of dyssynergia cerebellaris myoclonica.

In the case published by Daum and others (1953) there was only a generalized dysrhythmia without any of the characteristic manifestations of myoclonic epilepsy even after intermittent light stimulation. The patient of Alajouanine and others (1955) displayed only posterior theta waves at the rate of 6 c./sec., while De Risio's patient (1957) exhibited theta waves of low amplitude in bilateral temporal leads. In the latter patient, intermittent light stimulation as well as photo-cardiazol activation did not give rise to manifestations of myoclonic epilepsy. The youngest child of the P. family may be considered as having the disease in its initial stage (cerebellar disorders, generalized discharge determined by "largactil", bi- and triphasic spikes in the central region). The father may be affected with another syndrome of the group of cerebellospinal degenerations, but this is difficult to ascertain in the absence of anatomical data.

The delayed mental development in the children must be specially mentioned, particularly in the two brothers and in the mother.

In the case of Elisa, the myoclonus had no electroencephalographic accompaniments; nor were the generalized and synchronous spike-and-wave or polyspike-and-wave discharges accompanied by myoclonus in the sister and in the elder brother. Intermittent light stimulation did not cause either electroencephalographic discharges or clinical myoclonus. Such characteristics compel us to admit that there is a physiopathological difference between myoclonus in Hunt's disease and in myoclonic epilepsy. According to Greenfield (1954), there may be different types of myoclonia, but insufficiently studied. Discrepancies might be explained by different modalities of discharges from the focus. In our patient we have pointed out the antagonism existing between the action of "largactil" and that of adrenaline. In the case of Elisa, "largactil" almost completely abolished the myoclonus, but it exerted an untoward influence upon the electroencephalographic tracings, whereas adrenaline obviously aggravated myoclonus. In the case of Emmanuel, "largactil" determined the onset of clinical myclonus which was not present before. It might be inferred that myoclonus is determined by a hyperexcitable focus at the level of the mesodiencephalic reticula-

formation. Discharges towards the brain cortex induce the typical spike-and-wave or polyspike-and-wave alteration. Discharges towards the motor neurone in the anterior horn of the spinal cord produce clinical myoclonus. Each discharge from the focus is therefore directed towards the cortex and towards the spinal cord. We have pointed out before (Kreindler, Broşteanu, and Poilici, 1957) that in petit mal there is an analogous mechanism. In myoclonic epilepsy due either to a great reticular excitability or to the fact that the cortex and the peripheral motoneurone have the same degree of hyperexcitability, each discharge from the focus has cortical and peripheral accompaniments. The same phenomenon is sometimes liable to occur in myoclonic cerebellar dyssynergism (Cristophe and Rémond, 1951). Reticular dysfunction or different degrees of cortical and spinal excitability cause the discharge from the focus to have but a single accompaniment, *i.e.*, either cortical or peripheral. We are inclined to think that the cause is rather related to reticular dysfunction. Both "largactil" and adrenaline have a considerable reticular action, and in the two children they influenced the myoclonic discharges. In the case of Elisa, who displayed myoclonus, "largactil" exerted a beneficial influence upon the peripheral discharge whereas adrenaline aggravated it. In the case of Emmanuel, who had no peripheral discharges, "largactil" induced such discharges. In both of them "largactil" brought about an aggravation of electroencephalographic alterations and particularly of generalized spike-and-wave discharges. The interparoxysmal alterations in electrogenesis are due to lesions of the reticular substance while differences in tracings are related to different morphological and functional alterations of the reticular substance.

The importance of the excitability of the motoneurone in the clinical efficiency of discharges from the focus is evident from the fact that strychnine, a substance exerting a prevailingly spinal action, causes an aggravation of myoclonus.

It might therefore be inferred that the different clinical and electroencephalographical aspects of dyssynergia cerebellaris myoclonica are determined by the diversity of morphological and functional alterations in the reticular substance and cerebellum. Transition forms are found between cases with but one symptom and those displaying the full picture of the disease.

References

Alajouanine, T., Scherrer, J., Contamin, F., Marteau, R., and Calvet, J. (1955). *Rev. neurol.*, **93**, 577.

Cristophe, J., and Gruner, J. (1956). *Ibid.*, **95**, 297.

——, and Rémond, A. (1951). *Ibid.*, **84**, 256.

Daum, S., Lecasble, R., and Foncin, J. F. (1953). *Ibid.*, **89**, 287.

De Risio, C. (1957). *Riv. sper. Freniat.*, **81**, 941.

Greenfield, J. G. (1954). *The Spino-Cerebellar Degenerations*, p. 79. Blackwell Scientific Publications, Oxford.

Hunt, J. R. (1921). *Brain*, **44**, 490.

Kreindler, A., Broşteanu, R., and Poilici, I. (1957). *Stud. Cercet. Neurol.*, **2**, 461.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 238.

IS LUMBAR PUNCTURE HARMFUL IN MULTIPLE SCLEROSIS?

BY

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That lumbar puncture is detrimental in multiple sclerosis has been taught for many years; the origin of this belief and the evidence on which it is based are difficult to trace. The general warnings sometimes given in text-book accounts of contra-indications to lumbar puncture in this disease appear to depend chiefly on the familiar experience of an occasional instance in which clinical deterioration has followed the procedure. More recently, during the Sixth International Neurological Congress held in Brussels in July, 1957, Professor K. Henner stated firmly that lumbar puncture was contra-indicated in the disease (Henner, 1957). This view was at variance with my own experience, and served as a stimulus to consider the question more closely.

During a current survey of cases of multiple sclerosis in north-eastern England, during which 700 patients were personally interviewed and examined, enquiry was made as to whether lumbar puncture had been carried out at any stage of the illness, and also as to the course of the disease during the subsequent month. Of the patients questioned, rather less than half had been subjected to spinal puncture, and in 250 instances the information was considered sufficiently reliable for analysis. Of these, 231 patients reported their condition as unchanged, 14 patients reported improvement, and five patients considered that their condition had deteriorated. This retrospective information refers essentially to the patient's own assessment with regard to the month following spinal puncture, though in many instances this was authenticated by a record of objective findings. For what such enquiry is worth, it lends little support to the view that this procedure significantly affects the course of the disease.

The difficulty of controlled observation in multiple sclerosis is one with which every worker engaged in its study is familiar: a second phase of the enquiry involved a comparison in 100 cases of the apparent course of the condition during the month following lumbar puncture with the tempo of progression evident during similar periods 12 months earlier and 12 months later.

Of these 100 patients, in 81 there was no difference in the course of the disease during the month following lumbar puncture by comparison with that during a similar period a year earlier and a year later. In 19 cases significant differences were noted.

One patient showed very marked deterioration following lumbar puncture: in this case the disease showed steady but less dramatic progression during both the periods used for comparison.

Eight patients improved during the month following spinal puncture, and of these none had been similarly improving 12 months previously, when in four the condition was static and in four gradually progressive. A year later four were improving, in three the condition was static, and one patient was deteriorating.

Ten patients showed no definite change during the month following lumbar puncture. Twelve months previously none of these was improving, in two the condition was static, and eight were deteriorating. A year later one was improving, six were static, and in three the condition was gradually becoming worse.

Five of the 250 patients studied had been subjected to myelography: in no instance did this procedure perceptibly alter the patient's condition.

These results indicate that lumbar puncture has little effect on the course of multiple sclerosis, and that any apparent effect occasionally observed is as likely to be favourable as deleterious. The risks of overlooking clinically atypical compression of the spinal cord are well known. There is clearly no reason to withold the procedure in any case where the faintest suspicion of such a lesion arises.

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REFERENCE

Henner, K. (1957). *Excerpta med. (Amst.), Sect VIII*, **10**, Congress Issue, p. 40.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 239.

SLOWNESS IN SCHIZOPHRENIA

BY

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Slowness is an abnormality which has been regularly and reliably demonstrated by psychometric tests in patients suffering from all forms of mental illness (Shapiro and Nelson, 1955a). In a previous enquiry we found that it was present in some schizophrenic patients and that those with inappropriate affect showed a greater tendency to it than the others (Harris and Metcalfe, 1956).

Nufferno Speed Test

In this investigation we have used only the Nufferno speed test, which is designed to measure speed as distinct from general level of intelligence. It consists of 19 problems of the Thurstone letter-series type in each of which the patient is presented with series of letters and is required to add at the end of the series the letter which is appropriate to the sequence (Furneaux, 1955, 1956).

Every patient was tested on two versions of equal difficulty. In the first or unstressed version (AA) the patient is allowed to work at his own rate, but in the second or stressed version (AB) the examiner urges him to complete the task as quickly as possible. The score for each version is the mean of the logarithms of the times spent for the completion of the items correctly solved in each version. The higher the score, therefore, the slower the patient.

Several workers have applied this test to schizophrenic subjects and all report a tendency for them to be slower than normals (Nelson, 1953; Ogilvie, 1954; Shapiro and Nelson, 1955a, 1955b; Broadhurst, 1956). The forms of the test used have varied, however, according to the aims in view, so that it is difficult to compare results. For the AA unstressed version the range for an unselected normal population is from 0·6 to 2·1 and for the AB stressed version 0·5 to 1·8. Broadhurst gives the standard deviation for a group of normal adults as 0·32 on the AA version.

Nufferno Test and Affect

Further examination of the scores of our original group of patients (Harris and Metcalfe, 1956) showed that those of the patients whose affect was markedly inappropriate were grouped closely together in the slower part of the scale, whereas the scores of the patients with moderately inappropriate affect were scattered over a much greater range. Of the original 40 subjects attempting our test battery, one failed to complete the Nufferno tests satisfactorily so had to be discarded for our present purpose.

TABLE I

AFFECT TESTED BY UNSTRESSED VERSION OF NUFFERNO TEST

	Markedly Inappropriate Affect	Moderately Inappropriate Affect	Normal Affect
Range (mean log time)	1·054 to 1·390	0·698 to 1·686	0·924 to 1·195
Standard deviation	0·10	0·23	0·13

Aims of the Investigation

Our present aims were to find out whether length of illness or previous physical treatment exerted any influence on speed, whether the degree of slowness in the early part of the illness bore any relationship to the outcome, and whether the slowness varied with the patient's clinical state, *i.e.*, decreased or disappeared when he recovered. For these purposes to the original group of 39 subjects were added 14 more schizophrenic patients from the same hospital, all showing gross psychotic features of a kind which left the diagnosis in no doubt. The ages of this group of 53 patients ranged between 19 and 56 with a mean of 30. They were tested on a shortened version of the Wechsler-Bellevue test and the mean I.Q. for the group was 107.

Length of Illness

Twenty-three of our 53 patients had been ill for less than a year, two for over 20 years, and the remaining 28 for intermediate periods. In our previous paper we found no relationship between length of illness and a speed score obtained from the block design test of the Wechsler-Bellevue

series. However, Table II shows a trend for slowness in the Nufferno speed tests to increase with length of illness before testing.

TABLE II

SLOWNESS RELATED TO LENGTH OF ILLNESS

Length of Illness	Mean Log-time AA	Mean Log-time AB
Under 1 year (23 subjects)	1·107	0·970
Between 1 and 2 years (9 subjects)	1·198	0·999
Over 2 years (21 subjects)	1·211	1·065

The AA mean score of the patients with less than one year's illness is different from the mean score of the group with more than two years' illness and is also different from all the rest of the patients at a high level of statistical significance (respectively $P = 0{\cdot}05$ and between 0·02 and 0·05). AB scores are not significantly different. An analysis of variance showed no significant difference.

None of these patients were chronic mental hospital inmates, although some were chronic home invalids, so that stay in an institution cannot have been a factor.

On account of the possibility that this difference was due to the patients who had been ill for a longer period receiving more physical treatment than those whose illness had been shorter, we examined two groups matched for the amount of physical treatment which they had received; all the members of one group had been ill for less than one year and all the members of the other group had been ill for more than two years.

TABLE III

SCORES RELATED TO LENGTH OF ILLNESS (NINE PATIENTS IN EACH GROUP)

Length of Illness	AA Mean Log-time	AB Mean Log-time
Less than 1 year	1·132	0·985
Over 2 years	1·241	1·030

It will be seen from Table III that the results are consistent with the conclusion that the longer the illness, the slower the score, although the number of subjects is small and the differences are not statistically significant.

TABLE IV

RELATIONSHIP BETWEEN LENGTH OF ILLNESS AND SLOWNESS AND AFFECT (39 SUBJECTS)

Length of Illness	Markedly Inappropriate Affect		Moderately Inappropriate Affect		Normal Affect	
	AA	AB	AA	AB	AA	AB
Under 1 year	1·143	0·999	1·028	0·838	1·104	1·042
Between 1 and 2 years	1·234	1·204	1·040	0·858	1·221	0·975
Over 2 years	1·274	1·223	1·175	0·972	1·146	0·972

In an attempt to understand this relationship between length of illness and slowness we referred again to the three categories of affective incongruity into which 39 of our subjects had been classified.

Table IV shows that the relationship between length of illness and slowness holds good only for those patients who exhibit inappropriate affect.

Physical Treatment

Of our 53 subjects, 23 had had no physical treatment at all before testing. Of the remaining 30, 19 had had insulin coma alone, eight had had electroshock alone, two had had both insulin and E.C.T., two had had barbiturate comas alone, one had had cardiazol convulsions alone, one had had insulin coma and leucotomy, and one had had insulin coma and topectomy. It seemed important to distinguish those who had had physical treatment recently from those who had only had it at a remoter date and this has been done in Table V.

TABLE V

RESULTS IN PATIENTS TREATED PHYSICALLY ACCORDING TO TREATMENT DATE

	AA	AB
Physical treatment within past 6 months	1·186	0·994
Physical treatment but not within past 6 months	1·159	1·035
No physical treatment	1·149	0·984

It will be seen from Table V that patients who have received physical treatment tend to be slower, but the differences are not statistically significant. Several of those who had no physical treatment had severe illnesses of long duration, so that it is unlikely that this effect is to be explained by the worse or more chronic cases gravitating to the physically treated group. As far as it goes, this finding is in agreement with the results of an investigation into the effects of E.C.T. in states of depression (Shapiro, Campbell, Harris, and Dewsbery, 1958), but not with our own results using the block design speed score (Harris and Metcalfe, 1956), which is of course a very different measure from the Nufferno test.

Outcome of Illness

As Windle pointed out in his comprehensive review (Windle, 1952), no psychological test has given useful prognostic information in patients suffering from schizophrenic illnesses. Later work by the Columbia-Greystones group has encountered the difficulty that patients in the acute stage of the illness appear to give the opposite results with the tests that they use to patients in the chronic stage (Windle and Hamwi, 1953). As one frequently cannot determine whether a patient is in the acute

r chronic stage until the outcome of the illness is pparent, these tests are of little practical value. ecause of our findings that inappropriate affect, hich is itself related to a poor outcome, was ccompanied by slower scores on speed tests, we ad some grounds for hoping that the Nufferno peed test might prove effective from a predictive oint of view.

For this part of the investigation we selected 37 patients out of our group of 54, rejecting those with chronic illnesses whose condition had remained static for some years and only keeping those for whom the outcome was in doubt. These were interviewed by the psychiatrist (A.H.) a year after they had been tested and assessed according to their clinical and social state. At the time he made the assessment he was ignorant of the test results. During the 12-month follow-up period, of these 37 patients, 23 had insulin coma treatment, four had barbiturate coma treatment, one had E.C.T. and "largactil", and nine had no physical treatment. Of these nine, six had finished a course of insulin coma, one a course of barbiturate treatment, and one a course of cardiazol treatment a week or two before being tested for the first time. There is no evidence that the type of physical treatment given affected the outcome (Ackner, Harris, and Oldham, 1957).

With regard to their clinical state they were divided into three groups, namely, recovered, residual defect, and still psychotic, as defined in a previous paper (Ackner, Harris, and Oldham, 1957).

TABLE VI

CLINICAL OUTCOME IN THREE GROUPS

Clinical Outcome	AA	AB	Stress-gain Score
Recovered (9 patients)	1·108	0·992	0·114
Residual defect (5 patients)	1·137	1·010	0·127
Still psychotic (23 patients)	1·177	0·943	0·233

There is a trend towards the association of higher speeds on the unstressed version of the test with a more favourable outcome and of high stress-gain scores with unfavourable outcome but the difference between the scores of the patients who later recovered and the scores of those who did not does not attain a satisfactory degree of statistical significance and is too small to render it useful in prediction.

With regard to their social state they were also divided into three groups, namely, independent, socially dependent but out of hospital, and in hospital, as defined in the previous paper.

Again high speeds on the unstressed version are associated with a more favourable outcome, but not at a statistically significant level.

TABLE VII

SOCIAL OUTCOME IN THREE GROUPS

Social Outcome	AA	AB	Stress-gain Score
Independent (15 patients)	1·122	0·990	0·132
Dependent, ex-hospital (12 patients)	1·165	0·990	0·166
In hospital (10 patients)	1·192	0·894	0·298

The stress-gain score is the difference between the scores on the stressed and unstressed versions. Furneaux (personal communication) suggests that a high stress-gain score represents a lower degree of personal motivation as it indicates that the subject needs more inducement from the examiner to attain his best level of performance. He believes that this score is not related to intellectual achievement and is more related to temperament.

The mean stress-gain score of our group was much higher (0·19) than that of a group of university students (0·05) (Furneaux, personal communication). All but two patients were quicker on the stressed than on the unstressed version. The stress-gain score differentiates at a satisfactory level of statistical significance between the independent and the "in hospital" groups (t test, P between 0·02 and 0·05). However, when the most appropriate cutting-score is chosen to discriminate between these two groups three out of 10 of the "in hospital" group and four out of 15 of the independent group are wrongly classified. This overlap, meaning that 28% of the patients would be wrongly classified, is too great to enable the Nufferno stress-gain score to be used for the prediction of social outcome.

Change in Mental Speed after Clinical Improvement

We tried to find out whether speed increases when the patient improves. This bears on one of the fundamental questions about slowness, whether it is due to a constitutional factor or to impaired function as the result of disease. Six patients were retested one year or more after their initial test and after they had completely recovered. There was a very slight improvement in their score. This slight improvement was also evidenced by a control group of six similar patients who at the time of their second test were still psychotic. These six patients had all just had or were about to have physical treatment at the time of their first test. Because of the complicating effect of the physical treatment which these patients had received no conclusions are possible.

Discussion

The trends are mainly in the expected directions, although there is an absence of satisfactorily significant figures. Unexpected findings with regard

to the stress-gain score appear and focus attention on this hitherto neglected measurement. From observation during testing, it seemed that those who showed the higher stress-gain scores reacted more warmly to the examiner than those with the lower scores, who remained more aloof and remote. It may be a matter of motivation, as Furneaux believes, or simply that some degree of aloofness prevents friction between a schizophrenic and his environment and so is a social advantage.

Turning back to the group of 39 patients whose affect has been estimated, those with markedly inappropriate affect show significantly lower stress-gain scores than those with moderately inappropriate or normal affect.

TABLE VIII

SIGNIFICANCE OF LOWER STRESS-GAIN SCORES RELATED TO AFFECT

	Markedly Inappropriate Affect	Moderately Inappropriate Affect	Normal Affect
Stress-gain Score	0·070	0·147	0·148

The t test between the means of the markedly inappropriate affect and other two groups is significant at the 0·01 level.

There is an apparent paradox in that a low stress-gain is associated with a good outcome, at least socially, and also with inappropriate affect, which is known to be unfavourable prognostically. Various explanations can be suggested. Social factors are changing rapidly and the community will now accept psychotic patients who a few years ago would have become chronic mental hospital inmates. The success of chlorpromazine in promoting social recoveries indicates that a reduction in tension and volume of affect, which this drug produces, may be socially valuable. The difference between inappropriateness of affect and a diminution of affective response has been emphasized in our previous paper, but it is probable that they are not entirely unconnected. This particular group of patients is a small one and may be atypical in some respects. If we take the 19 patients who of the original 39 were followed up, it will be seen that the relationship between affective state and outcome is less clear cut than in the larger previously published series. (The other 20 were too chronically ill to be used for the prognostic study and so were not followed up.)

TABLE IX

OUTCOME AFTER ONE YEAR RELATED TO AFFECTIVE STATE

Outcome at End of 12 Months	Original Affective State		Normal Affect
	Markedly Inappropriate Affect	Moderately Inappropriate Affect	
Recovered	1	1	2
Residual defect	2	0	2
Psychotic	3	6	4

The criterion of outcome, condition at a fairly arbitrary point in time, which we were obliged to use for practical reasons, is a crude one. These results with the stress-gain scores call for further investigation, especially as they give some hope of information of value in the rehabilitation of patients.

The results with regard to the effect of length of illness fit in well with long-held psychiatric beliefs concerning the type of patient who is likely to deteriorate and the type which is not.

Summary

The influence of various factors on the mental speed of a group of schizophrenic patients was investigated by means of the Nufferno speed test. Longer duration of illness was associated with slower performance on the unstressed portion of the test, this being more definite in the case of those patients who also showed inappropriate affect. Patients who had had physical treatment tended to be slower on the unstressed portion of the test and those whose illness had a favourable outcome tended to be faster than the others. A significant relationship appeared between low stress-gain score and favourable social outcome. No satisfactory formula for predicting outcome on the basis of this test could be devised. An effort to correlate speed with disease and recovery failed because of the difficulty of finding patients who had gone through their illness without receiving physical treatment, since this latter formed a complicating factor which could not be allowed for.

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REFERENCES

Ackner, B., Harris, A., and Oldham, A. J. (1957). *Lancet*, **1**, 607.
Broadhurst, A. (1956). *Some Variables Affecting Speed of Mental Functioning in Schizophrenics*. Ph.D. Thesis, University of London.
Furneaux, W. D. (1955). *The Nufferno Tests*. Bull. Nat. Found. Educ. Res. Engl. Wales No. 6: 32.
—— (1956). *Manual of Nufferno Speed Tests*. London Nat. Found. Educ. Res. Engl. Wales.
Harris, A., and Metcalfe, M. (1956). *J. Neurol. Neurosurg. Psychiat.*, **19**, 308.
Nelson, E. H. (1953). *Experimental Investigation of Intellectual Speed and Power in Mental Disorders*. Ph.D. Thesis, University of London.
Ogilvie, B. C. (1954). *A Study of Intellectual Slowness in Schizophrenia*. Ph.D. Thesis, University of London.
Shapiro, M. B., Campbell, D., Harris, A., and Dewsbery, J. P. (1958). *J. Ment. Sci.*, **104**, 681.
——, and Nelson, E. H. (1955a). *Brit. J. med. Psychol.*, **28**, 239.
——, —— (1955b). *J. clin. Psychol.*, **11**, 344.
Windle, C. (1952). *Psychol. Bull.*, **49**, 451.
——, and Hamwi, V. (1953). *J. clin. Psychol.*, **9**, 156.

. *Neurol. Neurosurg. Psychiat.*, 1959, **22**, 243.

THE USE OF AN OBJECT SORTING TEST IN ELUCIDATING THE HEREDITARY FACTOR IN SCHIZOPHRENIA

BY

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Much evidence is now available as to the importance of the hereditary factor in the causation of schizophrenic psychoses. However, the mode of inheritance still remains doubtful, Luxemburger and Kallmann favouring a recessive, and Lenz a dominant type. Kallmann has consistently advanced the theory that a specific recessive gene transmits the disorder, but that its effects can be successfully resisted by a "non-specific and certainly multifactorial type of secondary genetic mechanism" (Kallmann, 1952). He further considers that

> "the factor for schizophrenia, even though recessive, may sometimes be expressed in a merely heterozygous condition, but only to the extent of schizoid personality changes. . . . Schizoid types may be either heterozygote with little resistance to an intermediate expressivity of their single gene, or strongly resistant homozygotes" (Kallmann, 1946).

If this theory is correct, both the parents of schizophrenics must be either heterozygous or homozygous with respect to this gene, and so may show these schizoid personality changes. It was therefore considered that it would be of interest to investigate the possibility that the parents of schizophrenics show schizoid features more commonly than a control population.

The Schizoid Personality

Kallmann himself leaves the concept of the "schizoid personality" undefined. Noyes (1953) describes it as

> "marked by incongruities of the feeling-life coupled, characteristically, with a poorly socialized personality. . . . Its contrasting affective poles are sensitiveness on the one hand and dullness or coldness on the other. . . . Often it is not clearly differentiated from the cyclothymic, between which and the schizoid there is a sliding scale."

Mayer-Gross, Slater, and Roth (1954) agree that this personality

> "has as its main characteristic the quality of shyness, extreme sensitivity, sometimes apparent emotional coldness . . .", but note in addition "tendencies towards a paranoid or fanatic attitude, towards the bizarre, eccentric or socially inappropriate modes of behaviour."

Henderson and Gillespie (1956) identify the schizoid with the "shut-in" personality and quote Farrar as distinguishing five main types:

> "(1) The backward type, lacking ambition, absent-minded; (2) the precocious type, bookish, serious; (3) the neurotic variety, selfish, and deceitful . . . with minor ailments; (4) the asocial, seclusive and day-dreaming; and (5) the juvenile, which never seems to grow up."

Though there is a considerable amount of agreement between the above definitions, utilizing them to decide whether a "schizoid personality" was present or absent in any particular person would be somewhat subjective. A more objective method of assessment was therefore sought for. For this reason a finding of Rapaport (1945) was followed up. He was investigating the performance of a clinical and a control group on a sorting test, and noted that by restricting his scoring to certain features he most clearly separated the schizophrenic from other clinical groups. But then a high percentage of persons in the control group with a "schizoid personality" also scored within this range of abnormality. Though he does not define what he means by "schizoid personality", he indicates that it includes persons with a "limited range of interests, a tendency toward some degree of withdrawal, an unusual lack of colourfulness . . ." This appears to share sufficient features with the above definitions to be accepted as the same concept.

It was therefore considered that a sorting test might provide a means for objectively estimating the presence of schizoid features in the personality.

Sorting Tests

The sorting test was first introduced by Vigotsky to study thought disorder in schizophrenia. Its rationale is described by Rapaport (1945):

> "Sorting behaviour, in response to the instruction to 'put together those objects which belong together' is an expression of concept formation. Sorting behaviour, wherein the subject compares objects that belong to the realm and objects that do not belong to the realm, gives the examiner an opportunity to assess how rigid and concrete (narrow), or how fluid, vague, and over-generalized (loose), the concept formation of the subject is.

However, the sorting tests have not been found of sufficient value by psychiatrists to have attracted widespread interest. This may be for two reasons. One is that the workers who utilized these tests in the study of thought disorder tended to ignore the clinical findings in this field, and employed rather the conclusions of Goldstein (1944) and Kasanin (1944) that in schizophrenia there is usually a reduction in abstract thinking and a tendency to think in more concrete terms. Yet when we examine the original work of Bleuler (1951), we find him advancing a different concept:

> "In schizophrenia the associations lose their connections. This disorder may interrupt a few, many, or most of the thousands of threads which direct our thoughts. As a result thought becomes unusual and often logically false. . . . Naturally no fruitful train of thought can come of associations based merely on habit, similarity, subordination, causality, and so forth; it is the goal-presentation that shapes a series of concepts into thought. . . . For example, the concept of water varies greatly with its context, as in chemistry, physiology, shipping, landscape, flood, power supply and so on. Every one of these special concepts is tied to our ideas by a different thread: no healthy person thinks of soda-water when a flood is sweeping his house away, nor of buoyancy when he wants to quench his thirst. . . . In normal persons only those ideas come to the foreground which fit the context."

Again we find Noyes (1953) describing this thought disorder thus:

> "Because of their origin in the unconscious, associations are broken, are led into bypaths, are fragmented, incongruous, do not progress, or are joined together through common affects rather than through conscious, logical connections. . . ."

Hence it seems that the feature stressed by clinicians as found in this thought disorder is the presence of illogical, inappropriate, or irrelevant associations. When a method of scoring sorting test performance was employed which gave weight only to the degree of irrelevance of the responses, a significant correlation was obtained between this score and a clinical estimation of thought disorder in schizophrenics, based on this concept (Lovibond, 1954). Henceforth when the term "thought disorder" is used in this article, it will be in this sense, *i.e.*, thinking which contains illogical, inappropriate, or irrelevant associations.

The other reason which may have contributed to the relative lack of value of this type of test may be precisely the one which makes it more useful in the present investigation, namely, that it indicates the presence of "schizoid" personality features rather than schizophrenia *per se*, as Rapaport's finding quoted earlier suggests.

The Present Investigation

The hypothesis is tested that the performance of the parents of schizophrenics on the object sorting test will differ significantly from that of control normals, in the direction of the performance of schizophrenics.

Description of the Test.—The sorting test employed was that described by Rapaport (1945). The test material consists of 33 common objects: a real and an imitation (miniature, plastic) knife, fork, and spoon, a pipe, a cigar, a cigarette, a red ball, a lock, etc.

The test itself has two parts. In the first part the subject is required to place with each of seven initial objects "all of those objects which belong with it". After he has completed his sorting he is asked, "Why do all these belong together?" In the second part the examiner consecutively places before the subject 12 different groups of objects, each group having a different essential characteristic in common, *i.e.*, they are all tools, toys, eating utensils, etc. The subject is asked each time, "Why do all these belong together?" The subject's grouping in the first part and his verbal responses in both parts are recorded.

Administration.—To retain comparability with the results of Lovibond, the test was administered in accordance with the instructions of Rapaport, with the additions introduced by Lovibond (1954).

Method of Scoring.—The method referred to above was employed in which only the degree of irrelevance of the response is scored. In brief, if the subject's reason as to why the group of objects belonged together was applicable to, or could be extended to, approximately half of the remaining test objects, it was regarded as at the first level of irrelevance and scored one point. For example, if he said that all the paper objects belonged together because they are all inflammable, the property of inflammability is shared by about half of the remaining test objects. If his reason was applicable to, or could be extended to, all the remaining test objects, it scored two points. For example, the response "because they are all found in a house" applied to any grouping, could equally well apply to all the test objects. If his reason was applicable to, or could be extended to, all, or practically all, of the inanimate objects of the universe, it scored three points, for example, the response "because they all originally came out of the ground". It should be noted that failure to see a relationship, or the use of concrete reasoning, is not scored, and so does not penalize the subject.

In the investigation referred to above, a score of more than 6 correlated significantly with the presence of "thought disorder" in schizophrenics determined clinically; a score of 6 or less, with its absence.

The Experimental Group.—This consisted of 20 parents of schizophrenic in-patients, both recently admitted and long-term (up to seven years as in-patients). The criteria for selection were:

(1) The patient showed clinically the presence of "thought disorder", as defined above. This might ensure a more homogeneous group of schizophrenics and more certain diagnosis.

(2) Both parents were able and willing to undergo testing, *e.g.*, they were able to speak English fluently

Also they were "normal" in the sense that they were not hospital patients, were carrying on an occupation in the community, and were not apparently suffering from any form of psychiatric illness.

The Control Group.—The control group employed by Lovibond (1954) consisted of 45 subjects, "normal" in the sense defined above.

Results

A summary of the major characteristics of the experimental and this control group, control[1], is shown in Table I.

TABLE I

MAJOR CHARACTERISTICS OF EXPERIMENTAL AND CONTROL GROUPS

Group	No. of Each Sex		Age in Years	Education in Years
	M.	F.		
Experimental n = 20	10	10	Mean 47 Range 39/63	Mean 9·0 Range 7/15
Control[1] n = 45	30	15	Mean 26·1 Range 16/50	Mean 8·8 Range 7/15
Control[2] n = 20	10	10	Mean 51·8 Range 39/71	Mean 10·0 Range 9/14

It will be noted that there is a considerable discrepancy between the mean age of the experimental and control[1] groups. However, the experimental group are not of an age when senile changes would have taken place to any significant extent, and I have not noted any differences in patterns of "thought disorder" between these age groups. Also Cameron (1944) concluded from his investigation that changes in thinking with age were distinct from the patterns found in "schizophrenic thought disorder".

To validate further the comparison of the performances of these two groups an additional control group was investigated, control[2]. A summary of the major characteristics of this group is also shown in Table I. It consists of 20 medical patients at or above the age of 39, chosen at random by the charge nurses of a male and a female ward in a London general hospital.

A comparison of the performance of these two control groups on the sorting test is shown in Table II.

TABLE II

RELATIONSHIP OF SCORES OF PERFORMANCE ON SORTING TEST OF TWO CONTROL GROUPS

	Control[1]	Control[2]	Total
Scores of 6 or less	41	18	59
Scores of more than 6	4	2	6
	45	20	65

As there is no significant difference between the performance of these two groups, their summated scores were employed in the comparison with the experimental group, as shown in Table IV.

The scores of the individual members of the experimental group are given in Table III.

TABLE III

SCORES OF PARENTS OF SCHIZOPHRENICS WITH "THOUGHT DISORDER" ON SORTING TEST

Patient	Mother	Father
1	7	0
2	7	16
3	10	0
4	14	2
5	3	14
6	0	8
7	4	10
8	11	9
9	0	10
10	6	13

It will be noted that in each of the 10 cases at least one parent had a score above 6, that is, a score which in schizophrenic patients correlated significantly with the presence of clinical "thought disorder". The significance of this finding was investigated by testing its relationship with the distribution of scores in the normal control group, as shown in Table III

TABLE IV

RELATIONSHIP OF SCORES OF PERFORMANCE ON SORTING TEST IN PARENTS COMPARED WITH CONTROLS

	Parents	Controls	Total
Scores of 6 or less	8	59	67
Scores of more than 6	12	6	18
	20	65	85

$P < 0.001$ (2 tailed).

The X^2 test with Yates' correction for small numbers shows the probability of the above groups having come from the same population is less than 0·1%. We can therefore conclude that the scores of parents of schizophrenics with "thought disorder" on the sorting test differ from those of control normals in the same direction as do those of the schizophrenic patients themselves.

Discussion

As this tendency to score highly on Rapaport's sorting test is found in a high percentage of the parents of schizophrenics as well as in schizophrenics themselves, it seems that this score may provide an objective measure of certain aspects of the "schizoid personality". If this is so, the finding of a score indicative of "schizoid" features in at least one of the two parents of every patient investigated would support Kallmann's concept quoted in the introduction, *viz.*, that the presence of the gene producing schizophrenia may be indicated in those people who successfully resist the disease by the production of a "schizoid personality". The

finding that the significant score was present in one parent in all cases, but in both only twice, might suggest a dominant rather than a recessive mode of inheritance. To take this as more than suggestive would be extremely rash, but it is worth following up. If confirmed, the discrepancy with Kallmann's conclusion might be explained by the more homogeneous nature of the schizophrenic patients investigated, only those with clinical "thought disorder" being selected. Mayer-Gross *et al.* (1954) suggest that the heterogeneity of schizophrenia may be one of the factors responsible for the present conflict of views as to the mode of inheritance of this disease.

It is of interest to speculate on the actual nature of the condition we are measuring with this test. Rapaport's statement that "sorting behaviour . . . is an expression of concept formation" would seem an acceptable one. When the scoring of performance on a test of sorting behaviour is restricted solely to the degree of irrelevance of the responses, it seems likely that we are dealing with an abnormality of concept formation in those people who score highly. That such an abnormality could contribute to the "bizarre, eccentric, or socially inappropriate modes of behaviour" (Mayer-Gross *et al.*, 1954) found in the "schizoid personality" is fairly certain.

Summary

A significant number of parents of schizophrenics with "thought disorder" were found to obtain scores on the sorting test of Rapaport (1945) different from those of control normals but similar to those found in schizophrenic patients.

It is suggested that this test may provide an objective means of estimating the presence of "schizoid" features in the relatives of schizophrenics, and thus aid in the elucidation of the hereditary factors in schizophrenia.

References

Bleuler, E. (1951). "The Basic Symptoms of Schizophrenia." In Rapaport, D. *Organization and Pathology of Thought*, p. 581. Columbia University Press, New York.

Cameron, N. (1944). "Experimental Analysis of Schizophrenic Thinking." In Kasanin, J. S. (ed.) *Language and Thought in Schizophrenia*, p. 50. University of California Press.

Goldstein, K. (1944). "Methodological Approach to the Study of Schizophrenic Thought Disorder." In Kasanin, J. S. (ed.) *Language and Thought in Schizophrenia*, p. 17. University of California Press.

Henderson, Sir D., and Gillespie, R. D. (1956). *A Textbook of Psychiatry*, 8th ed. Oxford University Press, London.

Kallmann, F. J. (1946). *Amer. J. Psychiat.*, **103**, 309.

—— (1952). "Genetic Aspects of Psychoses." In *The Biology of Mental Health and Disease*: 27th Annual Conference of the Milbank Memorial Fund, p. 283. Hoeber, New York.

Kasanin, J. S. [ed.] (1944). *Language and Thought in Schizophrenia*. University of California Press.

Lovibond, S. H. (1954). *Aust. J. Psychol.* **6**., 52.

Mayer-Gross, W., Slater, E. and Roth, M. (1954). *Clinical Psychiatry*. Cassell, London.

Noyes, A. P. (1953). *Modern Clinical Psychiatry*, 4th ed. W. B. Saunders, Philadelphia.

Rapaport, D. (1945). *Diagnostic Psychological Testing*, Vol. I. The Year Book Publishers, Chicago.

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A CLINICAL AND BIOCHEMICAL STUDY OF A TRIAL OF IPRONIAZID IN THE TREATMENT OF DEPRESSION

BY

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Iproniazid (isopropylisonicotinic acid hydrazide) is a compound with a marked antibacterial action against *M. tuberculosis*. Although a number of clinical trials have shown it to be effective against tuberculosis, side-effects are common, so that it has been largely superseded by the relatively non-toxic compound, isoniazid. As one of the more frequent of these side-effects is euphoria, several groups of workers have given iproniazid empirically to depressed patients and reported improvement.

There has been much speculation about the mechanism by which this benefit might be obtained but little direct corroborative evidence. It is known that iproniazid has a marked inhibitory action on monoamine oxidase (Zeller and Barsky, 1952), the enzyme largely responsible for inactivation of 5-hydroxytryptamine (5HT) (Sjoerdsma, Smith, Stevenson, and Udenfriend, 1955). A proportion of the naturally occurring catechol amines are also inactivated by this mechanism (von Euler, 1956). In the experimental animal, it has been shown that changes in the brain concentration of 5HT and catechol amines are associated with alterations in the behaviour of the animal. Thus, the decrease in brain concentration of these substances obtained after treatment with reserpine results in behaviour compatible with a state of depression (Brodie, Pletscher, and Shore, 1955; Carlsson, Lindquist, Magnusson, and Waldeck, 1958), whilst an increase, obtained by administration of a precursor substance, leads to excitement (Bogdanski, Weissbach, and Udenfriend, 1958; Carlsson *et al.*, 1958). Iproniazid similarly leads to increased brain levels, with associated excitement (Spector, Prockop, Shore, and Brodie, 1958).

In man, reserpine has a tendency to induce a state of depression (Lemieux, Davignon, and Genest, 1956; Deshaies, Richardeau, and Dechosal, 1957), and also liberates 5HT from its binding sites in platelets (Carlsson, Shore, and Brodie, 1957), although there have been no direct observations on brain tissue. Conversely, iproniazid, which may cause euphoria, causes increased concentrations of 5HT in human platelets (Pletscher and Bernstein, 1958). Furthermore, electroconvulsive therapy is established as a method of treatment for depression in psychiatric practice, and in animals temporarily increases the concentration of 5HT in the brain but not in other organs (Garattini and Valzelli, 1957).

Although there is no evidence to suggest that the depressive illnesses seen in clinical practice are due to a deficiency of 5HT or catechol amines, it is not unreasonable to postulate that any improvement obtained with iproniazid may be connected with altered concentrations of these substances. Despite some enthusiastic reports, the degree of benefit that can be obtained is difficult to assess from the literature, for, so far as we are aware, no attempt at a controlled trial has yet been published.

The present investigation was, therefore, designed to answer the following questions:—

(1) Does iproniazid benefit patients with depression?

(2) If so, can the patients who respond be differentiated clinically or biochemically from those who do not?

(3) In patients who respond to iproniazid, is the benefit due to changes in the concentrations in the brain of 5HT or of catechol amines?

Method

Fifty patients with depression (Table I) who had been considered suitable for electroconvulsive therapy were given iproniazid in doses of 150 to 450 mg./day for periods varying from two to 40 weeks. Placebo was substituted in certain cases. The first few patients were also given reserpine, $1\frac{1}{2}$ to $4\frac{1}{2}$ mg./day, seven to 10 days after starting iproniazid: this was found to be unnecessary and was discontinued. The degree of depression was assessed by weekly rating scales which were completed by the registrar in charge of the case, who was unaware when placebo tablets were being used (Table II). Patients were said to respond to iproniazid if the depression improved with treatment, relapsed when placebo was substituted, and improved again when iproniazid was reintroduced. Patients who improved with iproniazid but did not relapse when placebo was substituted had

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TABLE I

50 CASES OF DEPRESSION TREATED WITH IPRONIAZID

	Coincidental Improvement	Improvement due to Iproniazid	Not Improved
Number of patients	14	12	24
Age (yr.): Mean	53·5	44·7	49·6
Range	43-64	30-58	33-67
Sex	7M. 7F.	3M. 9F.	9M. 15F.
Hospital status (in-patient)	10	7	17
Family history of depression	1	1	5
Previous depressive illness	11	5	11
No depressive illness before age 45	3	4	9
Length of present illness	8 months	7½ months	21 months (12 exc. 2 cases)
Mean rating of depression (Table II)	3	2·7	3
Adverse prognostic features (marked hypochondriasis or depersonalization)	2	3	6
Aetiological factors of importance:			
Physical	4	1	6
Constitutional	9	9	15
Environmental	5	7	10

TABLE II

RATING SCALE

Mental Condition	Rating
Depression	0 Marked (actively wishes to die or no interest in living) 1 Mild 2 Not depressed 3 Elated
Retardation	0 Marked (needs constant nursing attention or encouragement to fulfil essential personal needs) 1 Mild 2 Not retarded 3 Overactive
Interest in social activities	0 Will not participate 1 Some participation with encouragement 2 Willing but passive participation, *e.g.*, spectator role 3 Willing and active participation

necessarily to be designated as "coincidental" improvement.

Early morning specimens of urine were collected before and at weekly intervals after treatment was started. 5-Hydroxyindoleacetic acid (5HIAA) was estimated as mg./g. creatinine by the method of Udenfriend, Titus, and Weissbach (1955). Creatinine was measured by a Lloyd's reagent absorption method (Hare, 1950). The identity of the 5HIAA was confirmed by the extraction procedure of Udenfriend *et al.* (1955), followed by two-dimensional paper chromatography (Jepson, 1955).

Results

(1) Does Iproniazid Benefit Patients with Depression?—Twenty-six of the 50 patients improved during treatment with iproniazid. Twelve of these were defined as having responded to iproniazid and 14 as having a "coincidental" improvement. Twenty-four patients did not improve (Table III). The improvement in patients defined as having responded to iproniazid usually began during the second and third weeks of treatment and this delay was not shortened by increasing the dose of the drug. There appeared to be no advantage in giving iproniazid in doses greater than 200 mg./day. On the other hand, some patients relapsed on dosage lower than 150 mg./day.

TABLE III

RESULTS

Cases improved	26
Improvement "due to iproniazid"	12
"Coincidental" improvement	14
Cases not improved	24

Side-effects of iproniazid at the dosage used in the present investigation were common. The most frequent were increase in weight, fluid retention, hypotension and postural hypotension, palpitations and throbbing headache, hesitancy of micturition, and impotence. The increase in weight was sometimes marked, up to 2 st. in two months. Studies with ^{24}Na have shown that this weight increase cannot be explained simply by water retention (Gibbons, J. L., and Pare, unpublished results). In this series there were no cases of peripheral neuropathy. One of the patients in our series died from acute hepatic necrosis (Pare and Sandler, 1959). When it became known that liver damage occasionally follows administration of the drug, standard tests of liver function were carried out routinely in 24 patients. Serum bilirubin, thymol turbidity, zinc sulphate turbidity, alkaline phosphatase, and serum proteins showed no significant abnormality. Estimation of serum glutamic-oxaloacetic transaminase activity which has recently come into extensive use as an index of hepatocellular damage was also carried out in 29 patients and showed significant changes in nine of them (Pare and Sandler, 1959).

By definition, patients who improved with iproniazid but did not relapse when placebo was substituted, were termed "coincidental" improvements. In the group defined as having responded to iproniazid, there was no evidence that iproniazid cut short their depressive illness, but rather that it provided symptomatic relief.

(2) Can Patients Responding to Iproniazid be Differentiated Clinically or Biochemically from Those Who Do Not?—Clinical assessment did not differentiate the patients who failed to improve with treatment either from patients who responded to iproniazid or from those who improved "coincidentally" (Table I). Estimations of urinary 5HIAA

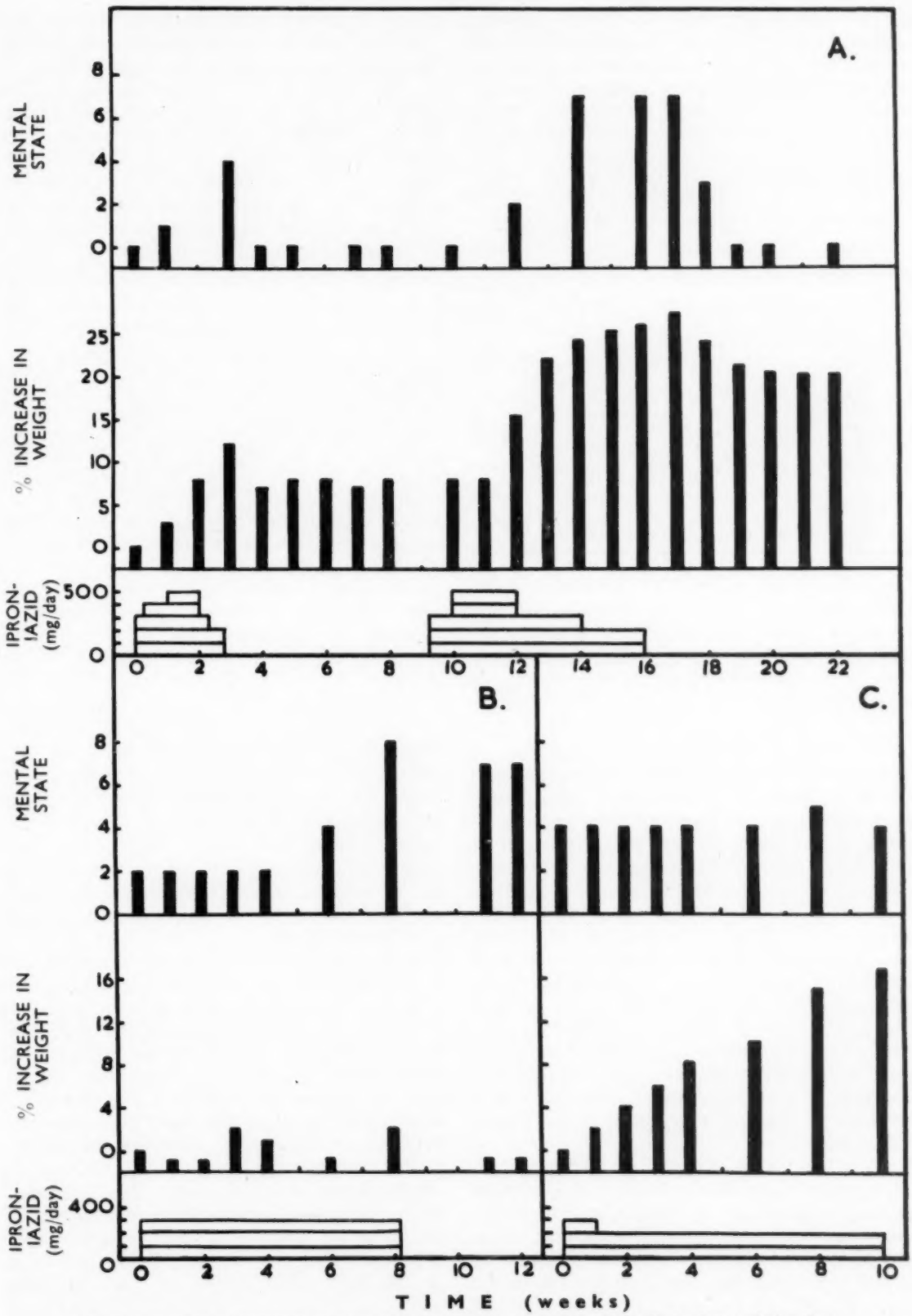

FIG. 1.—The effect of iproniazid on the weight and mental state ratings (Table II) in three typical patients.

A. Improvement due to iproniazid therapy.
B. Improvement coincidental to iproniazid therapy.
C. Not improved by iproniazid.

on 22 patients before iproniazid therapy appeared to differentiate between the groups (Table IV) and reached levels of significance when patients who responded to iproniazid were compared with those who did not.

TABLE IV

MEAN VALUES FOR URINARY 5-HYDROXYINDOLEACETIC ACID (5HIAA) IN EARLY MORNING SPECIMENS OF URINE COLLECTED BEFORE IPRONIAZID THERAPY

	5HIAA (mg./g. creatinine)	
9 patients improved "due to iproniazid"	3·0±0·50	P = <0·05
6 patients not improved with iproniazid	4·5±0·75	
7 patients improved "coincidentally" to iproniazid therapy	3·1±0·86	P = >0·1

TABLE V

MEAN VALUES FOR URINARY 5-HYDROXYINDOLEACETIC ACID (5HIAA) IN NINE PATIENTS BEFORE AND DURING ADMINISTRATION OF IPRONIAZID

	Mean 5HIAA (mg./g. creatinine)	
Before iproniazid	3·7 ± 0·74	0·1 > P > 0·05
During iproniazid	2·6 ± 0·46	

Concentrations in urine of 5HIAA from the nine patients examined before and during treatment were lower during iproniazid administration, although this fall did not reach statistical significance (Table V). No abnormal metabolites were seen on these chromatograms.

(3) In Patients Responding to Iproniazid, is Benefit Due to Changes in Brain Concentrations of 5HT, to Changes in Concentrations of Catechol Amines, or to Both?—In animals, both 5-hydroxytryptophan (5HTP) and 3, 4-dihydroxyphenylalanine (DOPA) are known to increase the brain concentrations of 5HT and catechol amines respectively (Udenfriend, Weissbach, and Bogdanski, 1957; Carlsson *et al.*, 1958). It is not quite clear which particular catechol amine concentration is increased during DOPA administration. Carlsson, Lindquist, Magnusson, and Waldeck (1958) claim to have detected an increase in dopamine which, they state, is present in considerable concentration in rabbit brain. They could find no increase in noradrenaline. Shore and Olin (1958), however, state that noradrenaline makes up the greater proportion of brain catechol amines.

Patients who were known to "respond" to iproniazid were given DL-5HTP and DL-DOPA by intravenous injection at intervals of at least a day, at the same time of the day, and in random order. Three patients were given the drugs in dosage of 12·5 mg. while receiving iproniazid but during the period of therapy before improvement was expected. Three patients were given the drug in the absence of iproniazid. In this group the dosage ranged from 25 mg. of each drug in a single injection to 150 mg. 5HTP and 275 mg. DOPA, each over a 48-hour period. Neither clinical nor psychological assessments (kindly done by Dr. J. C. Brengelmann) demonstrated any alleviation of the depression by either drug. In addition, one patient was given 5HTP and DOPA together, in doses of 12·5 mg. of each subcutaneously twice daily for 16 days. No improvement in the depression was noted clinically.

Discussion

A number of workers have used iproniazid in the treatment of depression (Smith, 1953; Ayd, 1957; Dally, 1958; Ferreira and Freeman, 1958; DeVerteuil and Lehmann, 1958; Symposium, 1958, on iproniazid), usually in a dosage of 100 to 200 mg./day. Of a total of 353 patients, 190 (54%) were said to have improved. Comparison with the present investigation is difficult, as we studied only those cases of depression which were considered suitable for electroconvulsive therapy. However, taking the total number of patients in the present investigation who improved, whether "coincidentally" or in response to iproniazid, the 52% improvement compares closely with those reported by other workers.

This alleviation from depression was bought at the price of side-effects which were pronounced and frequent and one patient died from acute hepatic necrosis. Although it is difficult to interpret the finding of a raised serum glutamic-oxaloacetic transaminase in almost 30% of our patients, we would suggest that any rise detected in routine weekly estimations should, in the present state of our knowledge, be treated as presumptive evidence of liver damage, and the drug be discontinued (Pare and Sandler, 1959).

In this investigation, as with others reported, there is a characteristic delay before improvement occurs. This delay is not shortened by increasing the dosage of iproniazid. The fact that neither 5HTP, DOPA, nor a combination of these two drugs, alleviated the depression in patients who responded to iproniazid does not support the suggestion that the drug acts directly by increasing the brain concentrations of 5HT or catechol amines. However, the 5HTP and DOPA may have been given to our patients in too small a dosage or for too short a period of time, for the pre-treatment concentrations of urinary 5HIAA tended to be lower in patients who subsequently improved. However, we were unaware at the time of the high concentration of 5HT in bananas

Anderson, Ziegler, and Doeden, 1958) which were not excluded from the patients' diet. Our readings may not, therefore, be a true index of endogenous 5HT metabolism.

One of the many possible explanations of its action is that iproniazid allows the diversion of certain metabolic processes through alternative pathways. In animals given large doses of iproniazid, Weissbach, Redfield, and Udenfriend (1958) reported that an O-glucuronide conjugate of 5HT appears in the urine, but this detoxication product is likely to be inert. In the present investigation, and using much smaller doses of iproniazid than those used in animals by Weissbach *et al.* (1958), we were unable to find any abnormal metabolites.

Perhaps of most interest is the question whether iproniazid is a general euphoriant or whether it acts only on patients whose depression is due to a specific metabolic abnormality which has yet to be identified. The striking response to iproniazid noted in some patients compared with the apparent ineffectiveness of the drug in others suggests that the latter may be true.

Summary

A controlled trial of iproniazid on 50 patients with depression showed that 26 of them improved and that the improvement in at least 12 of these was due to the drug. The danger of liver damage was stressed.

An attempt was made to differentiate these groups and to determine the mode of action of iproniazid in those patients who responded. Methods used included parenteral administration of 5-hydroxytryptophan and 3, 4-dihydroxyphenylalanine and assessment of urinary 5-hydroxyindole excretion.

We are grateful to Professor A. J. Lewis and the physicians at the Bethlem Royal and the Maudsley hospitals for their cooperation in this trial; to Miss Lilith Emslie and Miss Doreen Crabtree, Royal Free Hospital, for skilled technical assistance, and to the Royal Free Hospital Endowment Fund and Roche Products Limited, for defraying their respective salaries; we are also grateful to Dr. J. Marks of Roche Products Limited for a generous supply of "marsilid" tablets and placebo, and for his advice.

References

Anderson, J. A., Ziegler, M. R., and Doeden, D. (1958). *Science*, **127**, 236.
Ayd, F. J. (1957). *Amer. J. Psychiat.*, **114**, 459.
Bogdanski, D. F., Weissbach, H., and Udenfriend, S. (1958). *J. Pharmacol.*, **122**, 182.
Brodie, B. B., Pletscher, A., and Shore, P. A. (1955). *Science*, **122**, 968.
Carlsson, A., Shore, P. A., and Brodie, B. B. (1957). *J. Pharmacol.*, **120**, 334.
——, Lindquist, M., Magnusson, T., and Waldeck, B. (1958). *Science*, **127**, 471.
Dally, P. J. (1958). *Brit. med. J.*, **1**, 1338.
Deshaies, G., Richardeau, N., and Dechosal, F. (1957). *Ann. méd.-psychol.*, **115**, 417.
DeVerteuil, R. L., and Lehmann, H. E. (1958). *Canad. med. Ass. J.*, **78**, 131.
Ferreira, A. J. deL., and Freeman, H. (1958). *Amer. J. Psychiat.*, **114**, 933.
Garattini, S., and Valzelli, L. (1957). In *Psychotropic Drugs*, p. 428. Ed. Garattini, S., and Ghetti, V. Elsevier Publishing Co., Amsterdam and London.
Hare, R. S. (1950). *Proc. Soc. exp. Biol. (N.Y.)*, **74**, 148.
Jepson, J. B. (1955). *Lancet*, **2**, 1009.
Lemieux, G., Davignon, A., and Genest, J. (1956). *Canad. med. Ass. J.*, **74**, 522.
Pare, C. M. B., and Sandler, M. (1959). *Lancet*, **1**, 282.
Pletscher, A., and Bernstein, A. (1958). *Nature (Lond.)*, **181**, 1133.
Shore, P. A., and Olin, J. S. (1958). *J. Pharmacol.*, **122**, 295.
Sjoerdsma, A., Smith, T. E., Stevenson, T. D., and Udenfriend, S. (1955). *Proc. Soc. exp. Biol. (N.Y.)*, **89**, 36.
Smith, J. A. (1953). *Amer. Practit. Dig. Treatment*, **4**, 519.
Spector, S., Prockop, D., Shore, P. A., and Brodie, B. B. (1958). *Science*, **127**, 704.
Symposium on the Biochemical and Clinical Aspects of Marsilid and other Monoamine Oxidase Inhibitors (1958). *J. clin. exp. Psychopath.*, **19**, Suppl. 1.
Udenfriend, S., Titus, E., and Weissbach, H. (1955). *J. biol. Chem.*, **216**, 499.
——, Weissbach, H., and Bogdanski, D. F. (1957). *Ibid.*, **224**, 803.
Von Euler, U. S. (1956). *Noradrenalin*. C. C. Thomas, Springfield, Illinois.
Weissbach, H., Redfield, B. G., and Udenfriend, S. (1958). *Fed. Proc.*, **17**, 418.
Zeller, E. A., and Barsky, J. (1952). *Proc. Soc. exp. Biol. (N.Y.)*, **81**, 459.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 252.

A CEREBROSPINAL FLUID BANK*

BY

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It has been found relatively simple to establish a cerebrospinal fluid bank. Spinal fluid removed at the time of pneumoencephalography may be preserved under sterile conditions by freezing and later used for replacement of cerebrospinal fluid lost at operation.

The importance of the composition of solutions used to irrigate the brain or replace lost cerebrospinal fluid has been known for a long time. Forty years ago, Flexner and Amoss (1917) showed that intraspinal injection of normal saline, Ringer's or Locke's solutions increased the susceptibility of monkeys to polio virus while the reinjection of spinal fluid from other animals did not regularly do so and the reinjection of autogenous spinal fluid never did. Weed and Wegeforth (1919) reported that irrigation of the subarachnoid space in cats with a modified Ringer's solution produced no apparent ill-effects while irrigation with normal saline produced severe disturbances, convulsions, states of acute mania, and often death. Kasahara (1924) studied the effect of different solutions on the spinal subarachnoid space of rabbits using the cerebrospinal fluid cell count as the criterion. He found that 0·6 to 0·7% sodium chloride solutions were less irritating than other concentrations of saline. Ringer's solution was less irritating than 0·7% saline and human cerebrospinal fluid was the least irritating of any substances used.

In 1934, Hartmann reported a method of preparing an artificial spinal fluid which Sachs (1945) used for replacement of spinal fluid lost from the ventricles at the time of operations for hydrocephalus. The preparation of this carefully buffered fluid required the preparation of two separate solutions which were separately sterilized and mixed just before using. Apparently the use of this fluid never became widespread, perhaps because of the technical difficulties of preparation.

Elliott and Jasper (1949) studied the effects of irrigating fluids on the pial blood vessels of cats. They described the preparation of two sterile solutions for irrigation of the brain during operation and the replacement of fluid lost from the ventricles. One of these was a modified Ringer's solution, the other closely resembled Hartmann's solution but was more easily prepared. Lewis and Elliott (1950) later described the clinical use of this latter fluid, Solution B of Elliott and Jasper.

It occurred to one of us (H.C.V.) that human cerebrospinal fluid removed at routine pneumoencephalography might be kept sterile and preserved by freezing. An ample supply of such fluid would then be available for the replacement of fluid lost from the ventricles at operation and for the actual irrigation of exposed brain tissue during operation.

Initial studies were performed on specimens of human spinal fluid collected at the time of pneumoencephalography. These were frozen and stored for varying periods of time at −10°C. Chemical analyses of the spinal fluid were made at the time of collection and aliquots were then taken for analysis at monthly intervals during the period of storage. Sodium and potassium concentrations were determined with an internal-standard type flame photometer (Baird Associates), chloride by the method of Schales and Schales (1941), and *p*H with a Beckman *p*H meter. Total osmotic activity of the spinal fluid was determined by the measurement of the freezing point depression (Fiske Associates).

Table 1 summarizes the results obtained. In each case the first figures represent the values obtained at the time of initial analysis. Interim determinations performed at four-week intervals did not differ significantly. It will be noted that initially the values for the *p*H are higher than those usually observed in normal blood serum. This undoubtedly occurred because no precautions were taken to prevent the loss of carbon dioxide from the spinal fluid. On freezing and thawing the fluid at the time of later analyses the value for the *p*H rose further, probably because of a similar mechanism with further loss of carbon dioxide.

Technique

Since the chemical and physical characteristics of the fluid did not appear significantly altered by freezing and

*Read before the Chicago Neurological Society on March 11, 1958.

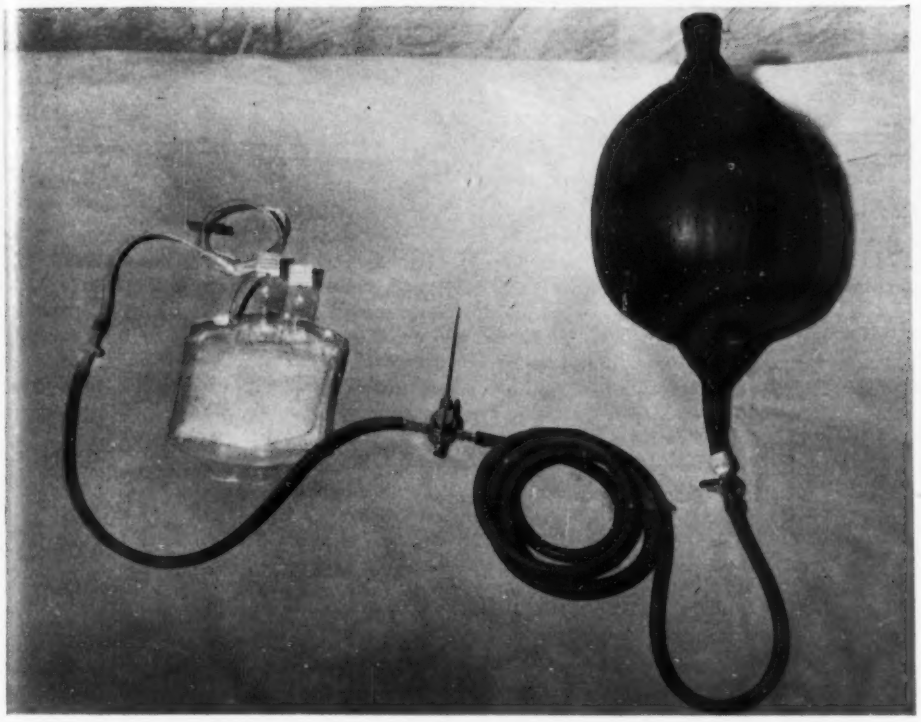

FIG. 1.—Photograph of apparatus used for collection of human cerebrospinal fluid. The plastic container for the fluid, the oxygen container, spinal puncture needle, four-way stopcock and connexions are shown. The 10 ml. Luer-Lok syringe is not shown.

prolonged storage, a cerebrospinal fluid bank has been developed for clinical use. Sterile plastic containers* of 300 ml. volume made originally for the collection and storage of citrated blood are used for the collection of the fluid (Fig. 1). Pneumoencephalography is carried out with the patient in the sitting position (Fig. 2). After lumbar puncture has been performed, the manometric pressure is determined. A specimen of fluid is taken for routine laboratory examination and culture. Unless the fluid is grossly clear, no effort to collect it is made. Specimens of fluid which become contaminated by blood during collection are discarded.

If it is decided to collect the cerebrospinal fluid for storage, a four-way Lundy stopcock shown in the diagram (Fig. 3) is attached to the lumbar puncture needle. A sterile connexion with a reservoir of O_2 gas is made. Another sterile connexion is made with the sterile plastic container and a fourth connexion with a sterile 10 ml. syringe. Now cerebrospinal fluid is withdrawn into the syringe in 5 to 10 ml. increments. These increments are injected into the storage container. Similar increments of O_2 are aspirated into the syringe and then injected into the spinal needle. The alternate aspiration of spinal fluid and injection of O_2 is carried out until the operator is satisfied that good visualization of the ventricles and subarachnoid spaces will be obtained radiologically. Usually 100 to 160 ml. of fluid is removed. The apparatus is then dismounted, the needle removed, and the patient taken to the *x*-ray department for the usual radiological examination.

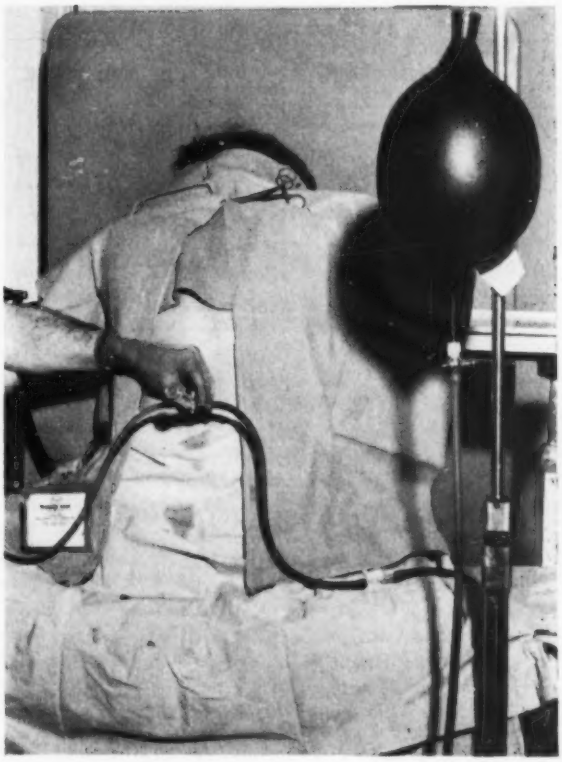

FIG. 2.—Photograph of patient and equipment for the collection of cerebrospinal fluid at the time of pneumoencephalography.

*Fenwal Transfer Pack, catalogue number TA-2 manufactured by Fenwal Laboratories, Framingham, Massachusetts.

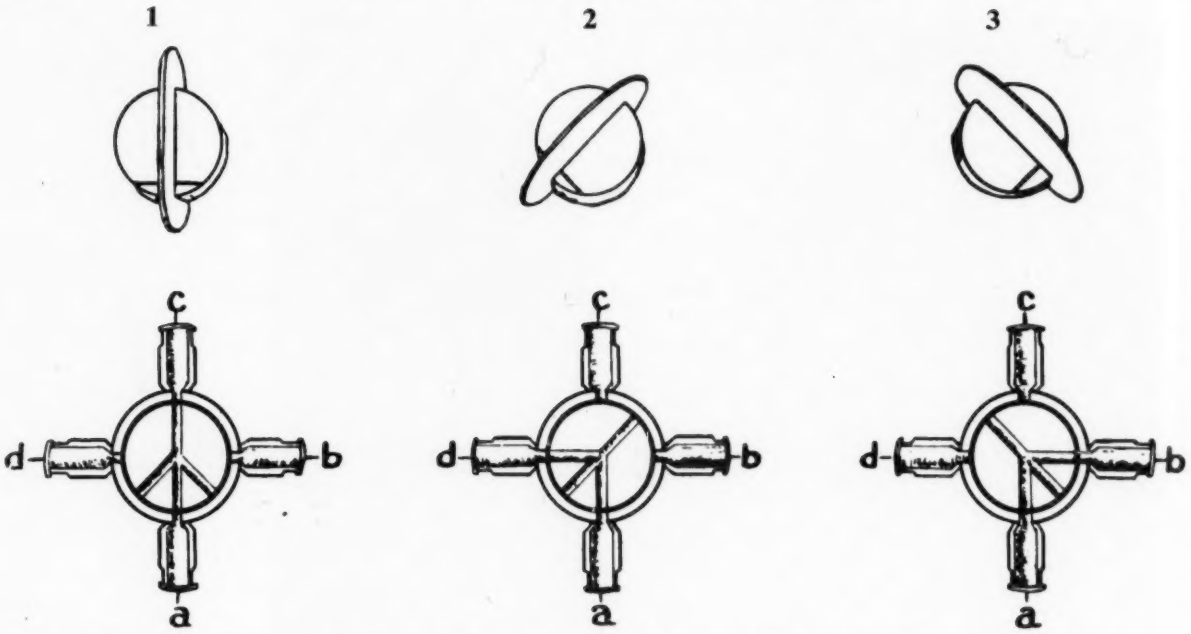

FIG. 3.—Cut-away diagram of Lundy four-way stopcock for the aspiration and collection of cerebrospinal fluid and the injection of oxygen. The 10 ml. Luer-Lok syringe is attached at (a). A Luer-Lok adaptor is used to connect the oxygen container to (b). Another Luer-Lok adaptor connects (d) to the plastic container for the cerebrospinal fluid. A short segment of rubber tubing with two Luer-Lok adaptors connects (c) to the spinal puncture needle. The direction of rotation of the stopcock is shown above the cut-away diagram for each position. Position 1 is used for the aspiration of fluid and the injection of oxygen. Position 2 permits the injection of fluid from the syringe into the plastic container. Position 3 allows aspiration of oxygen into the syringe.

TABLE 1

COMPOSITION AND BACTERIAL STATE OF SAMPLES OF C.S.F.

Specimen	Date	*p*H	Na−	K−	Cl−	Osmolarity (m.osm./litre)	Culture
			(m.Eq./litre)				
Bel	6/12/56	7·60	145	3·06	136	281	No growth
Bel	7/18/56	7·70	141	2·90	134	279	No growth
Gut	8/28/56	7·50	147	2·94	123	271	No growth
Gut	12/7/56	7·70	144	2·99	123	271	No growth
Ruf	4/9/57	7·54	146	2·90	122	270	No growth
Ruf	6/4/57	7·68	149	3·00	124	277	No growth

The container of cerebrospinal fluid is labelled and placed in the freezer at −20°C. If any abnormalities are found on laboratory examination of the fluid or if the culture shows bacterial growth, the collected fluid is discarded. Otherwise it is kept until it is needed for use. At that time the container is removed from the freezer and the fluid thawed at room temperature. It is then emptied into a sterile basin and warmed to 100°F. in a water-bath. A culture is taken before the fluid is used for irrigation or replacement. If such a culture should show bacterial growth, sensitivity studies would be made and appropriate therapy instituted. To date such a contingency has not been encountered.

The use of human cerebrospinal fluid in brain operations from a cerebrospinal fluid bank has proved practical. To date, there have been no complications. Human cerebrospinal fluid is superior to artificial fluids. Wherever a tissue bank is in operation, the collection and preservation of the fluid is simpler than the preparation of complicated solutions, even one as simple as Solution A of Elliott and Jasper (1949). On most neurosurgical services, an ample supply of cerebrospinal fluid can be obtained from patients subjected to routine diagnostic pneumoencephalography.

REFERENCES

Elliott, K. A. C., and Jasper, H. H. (1949). *J. Neurosurg.*, **6**, 140.
Flexner, S., and Amoss, H. L. (1917). *J. exp. Med.*, **25**, 525.
Hartmann, A. F. (1934). *J. Amer. med. Ass.*, **103**, 1349.
Kasahara, M. (1924). *Amer. J. Dis. Child.*, **28**, 407.
Lewis, R. C., and Elliott, K. A. C. (1950). *J. Neurosurg.*, **7**, 256.
Sachs, E. (1945). *The Care of the Neurosurgical Patient*, p. 202 Mosby, St. Louis.
Schales, O., and Schales, S. S. (1941). *J. biol. Chem.*, **140**, 879.
Weed, L. H., and Wegeforth, P. (1919). *J. Pharmacol.*, **13**, 317.

BOOK REVIEWS

The Nature of Experience: Riddell Memorial Lectures, Thirtieth Series. By Sir Russell Brain. (Pp. 73. 8*s*. 6*d*.) London: Oxford University Press. 1959.

Sir Russell Brain gave the Riddell Memorial Lectures at Durham University, and they are reprinted in this book. He recapitulates the reasons for believing that the external world is not as we perceive it, employing among other examples of this discrepancy, the amputee's phantom limb, first quoted in this connexion by Descartes, and the perceptual changes that occur with mescaline. He comes down plainly in favour of the sense-datum view of perception, that an external physical world exists and that what we perceive is a private perceptual world constructed by the activity of our own brain. In the latter the physical world is modified not only by the multiplicity of coding and recoding of sensory information in the nervous system, but also by factors external to our bodies. For instance, due to the time taken by light to reach us, the stars of our perceptual world are very different both in space and time from the stars of the physical world. Sir Russell draws an apt analogy with radar in which the radar screen is regarded as analogous to the perceptual world.

He finally explores the consequences of this view for the nature of art. He argues that a work of art is "an image of feeling", that is, a physical embodiment of the feelings present in the artist's perceptual world, and that it will create in others a perceptual object embodying to a greater or less extent the feelings in the artist's perceptual world which led him to create the work of art. This theme is pursued and expanded, and used to explain and justify "modern" art, both visual and poetic, and to consider some of the problems of religious experience.

Sir Russell is, he says, very much aware of his amateur status as a philosopher. It is, however, essential that specialists in biological and physical sciences should make their contribution to philosophy, and it is possible that it will be in this way that philosophy regains its reputation as a subject with which every educated person must be acquainted.

Clinical Neurophysiology. By John Marshall. (Pp. viii + 296; 159 figures. 37*s*. 6*d*.) Oxford: Blackwell Scientific Publications. 1959.

The dependence of neurology on the basic sciences of anatomy and physiology becomes very apparent when one tries to understand physical signs and a rational approach in therapy. Dr. Marshall's book is a clear, straightforward account of those advances and trends in neurophysiology which significantly expand and clarify neurological knowledge. The chapters follow a fairly conventional pattern beginning with the nerve impulse and ending with the special senses. The facts are put together in such a way that one can always follow the evolution of an idea, and the choice of illustrations from the literature is particularly successful. On the whole the book is well up to date but the chapters on the cerebral cortex are rather conservative and not particularly informative.

Everyone interested in neurology will read this well produced book with great pleasure and profit even though it must be an interim report of a rapidly advancing science. The book is intended for clinicians primarily, but senior medical students could derive from it much benefit and a clearer understanding of the science of neurology.

Physiologie du Systeme Nerveux Central, 3rd ed. By Georges Morin. (Pp. 396; 104 figures. Fr. frs. 3,400.-.) Paris: Masson. 1958.

The third edition of this textbook has corrected several notable omissions of the previous editions: in particular, the role of muscle spindles in proprioceptive reflexes is at last discussed.

This is a clearly written book on neurophysiology, and is well illustrated and attractively produced. It also keeps firmly in mind the needs of medical students, for whom the book is written, and its clinical sections are admirably done, including a short chapter on the E.E.G.

Ein binauraler Hörsynthese-Test zum Nachweis zerebraler Hörstörungen. By J. Matzker; Foreword by H. Leicher. (Pp. x + 117; 46 figures. DM 19.80.) Stuttgart: Georg Thieme. 1958.

This monograph puts forward a proposal to apply binaural stimulation to the diagnosis of cerebral disorder. Dr. Matzker's test consists in feeding to the two ears speech divided into two frequency bands so chosen that what is heard by each ear separately is unintelligible, while the combination of the two inputs can be understood by the normal individual. In practice the band from 500 to 800 c.p.s. is fed to one ear and that from 1,500 to 2,400 to the other, all other frequencies being suppressed. It is argued that failure to effect the synthesis must be due to interruption or disturbance of the brainstem and thalamic pathways by which stimuli from both ears are brought to converge on each half of the cortex.

Results of the test on 750 neurologically normal subjects show a proportion of failures which varies with age. In children under 14, 34% fail, a percentage which drops to 2 or 3 between the ages of 20 and 60 and then rises rapidly into old age where over 90% of the subjects fail. The author accounts for this by the supposition that in the old the essential ganglion cells degenerate, while in the young these midbrain pathways are not yet "ground-in". As he rightly says, these findings demand that the test results on cases suspected of cerebral pathology be judged in accordance with the age

of the patient. Applied to patients exhibiting a variety of intracranial disorders, the test gave a positive result in a proportion of cases varying from 84% for tumours, through 58 in hypertension to 30 in epilepsy.

Unfortunately there is no evidence, only the author's *a priori* conviction, that such failure has anything special to do with disturbance of the pathways responsible for convergence of the two inputs onto each hemisphere. The localized lesions in those cases where the pathology could be established were very variously situated. In only two cases so far, both of metastatic carcinoma, have brain-stem lesions been detected. In both the damage was microscopic, and naked-eye pathology was apparent elsewhere in the brain. The binaural test result cannot itself afford any lateral or other localizing indication, and the data from the pathological cases reported show only that cerebral disorder tends to disturb the capacity to synthesize two separate, individually unintelligible, auditory signals from the two ears. This is perhaps hardly surprising, considering how common it is to find that any stepping-up of the difficulty of a high-grade task imposed on a damaged cortex reveals its defect. It is also quite in keeping with the test results on young and old. This particular test seems to suffer from the disadvantage, not entirely shared by some others, that it is uninformative as to the whereabouts of the lesion. Nevertheless the idea of using binaural stimulation in the study of cerebral disorder is a stimulating one, and for his emphasis on this we may be grateful to Dr. Matzker.

Pathogenesis and Treatment of Parkinsonism. 6th Annual Scientific Meeting of the Houston Neurological Society, Texas. Compiled and edited by W. S. Fields. (Pp. x + 372; illustrated. 81*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

This book, a verbatim report of a symposium by 24 authors, sets out to deal with the pathogenesis and treatment of Parkinsonism. The greater part of it is devoted to the techniques, results, and neurophysiological implications of artificially produced lesions in the region of the basal ganglia in man and in animals.

The first half of the book presents the known facts of animal experiment, namely that tremor and rigidity may be produced with difficulty in some animals by lesions, either stimulating or destructive, of the midbrain tegmentum and may be abolished by destructive lesions of the globus pallidus or corticospinal tracts. On these facts are based a number of interesting and ingenious theories, notably by Ward, on the site and mode of production of tremor and rigidity.

The second half of the book is a valuable review of the various surgical methods, past and present, used in the relief of Parkinsonism with a thoughtful chapter on selection for surgery by Schwab. Cooper's preference is for neuropallidectomy or chemothalamectomy by the balloon-alcohol method and his results, based on over 700 cases, including 50 bilateral operations, are impressive (symptomatic relief 80%; mortality 2·4%; hemiplegia 3%). Meyers reports a few cases treated with ultrasound, a method capable of producing small and precisely localized lesions. Even in the best hands only 10 to 15% of patients with Parkinsonism are suitable for surgery and it is strange that drug treatment should receive such scant attention.

Biochemistry and the Central Nervous System, 2nd ed. By Henry McIlwain. (Pp. vii + 288; 44 figures. 45*s*.) London: J. & A. Churchill. 1959.

This is the second edition, extensively revised, of this admirable book. Together with the author's volume on chemotherapy and the nervous system the two books form a most suitable and up-to-date review of the biochemistry of the central nervous system for neurologists and neurophysiologists. In this edition a quarter of the work quoted has been published in the last four years. The scope of the book is wide and such sections as those on hypoglycaemia, anticonvulsants, Wilson's disease, and the chapters on chemical factors in nervous transmission and depressants and excitants all provide concise information on subjects of direct interest to the clinician. The last chapter is on the brain and the body as a whole. We look forward in future editions to the proportionate increase in the length of this chapter relative to the rest of the book as the synthesis of knowledge progresses.

Biology of Neuroglia. Compiled and edited by William F. Windle. (Pp. xiv + 340; 78 figures. 63*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

The increasing attention being given to the function of neuroglia cells is reflected in this report of a "Conference on the Biology of Neuroglia" which was held in March, 1956. The volume is a very fine production with wonderful illustrations, and will be invaluable to those who wish to know what is happening in this remarkable field of research.

Nourishing Brain Cells. By C. E. Lumsden. (Pp. 23; 14 figures. 2*s*. 6*d*.) Leeds University Press. 1959.

This is Professor Lumsden's inaugural lecture. He gives an interesting account of what is known of the function of the neuroglia.

Le Syndrome de Guillain-Barré. By R. Coirault, A. Larcan, and P. Davidou; Foreword by Prof. P. Garcino. (Pp. 200. Fr. fr. 2,000.-.) Paris: Masson. 1958.

This book reviews the clinical and aetiological features of 46 cases of the Guillain-Barré syndrome. As the authors repeatedly stress, all their cases had acute polyradiculoneuritis with increased albumin content of the cerebrospinal fluid and no increase in the cell content. The authors argue that the picture of the Guillain-Barré syndrome has been confused, especially in the "Anglo-Saxon literature", by reports that include under this name transitional or even frankly distinct disorders. They believe that "idiopathic" cases are less common than secondary cases, and give as possible causes physical agencies, including fatigue and infections due to leptospira as well as viruses and bacteria, and occasionally even blood diseases. From the multiplicity of the apparent

causes they conclude that the aetiology may not be identical in every case even if the pathogenesis is the same.

Sequelae of Primary Aseptic Meningo-encephalitis. By Ragnar Müller, Ingvar Nylander, Lars-Erik Larsson, Lennart Widen, and Marianne Frankenhaeuser. (Pp. 115; illustrated.) Copenhagen: Ejnar Munksgaard. 1958.

This short monograph reviews 238 cases, children and adults, of aseptic meningo-encephalitis, and compares them with a control group of 138 matched patients who have not had the disease. The patients had a slightly greater number of headaches and E.E.G. abnormalities, and two had epilepsy, tonic pupils, and endocrine disorders respectively. In a few adults mild mental symptoms (lack of concentration and affective disorders) were noted. On the whole, however, no permanent sequels seemed to follow the disease, which can therefore still be described as benign.

Differentialdiagnose Neurologischer Krankheitsbilder. Edited by G. Bodechtel. (Pp. xxviii + 975; 533 figures. DM. 120.-.) Stuttgart: Georg Thieme. 1958.

Neurology is by tradition more an exercise in diagnosis than anything else, but this tradition is changing so quickly that it is somewhat surprising to receive this monumental work on differential diagnosis alone. The size of the book and the 12 contributors indicate the wonderful thoroughness with which the field has been covered.

The painstaking inclusion of every possible lesion makes this a most useful work of reference for the practical physician. Thus, as an example, under polyneuritis, there are nearly 90 sub-headings in the index. The many hundreds of illustrations are of exceptionally fine quality, and must represent the collection of a life time.

This type of book is of course of only limited interest to the research worker as the references are often inadequate, but there is no pretence here of adding to existing knowledge, only an enormous accumulation of information which is clearly of very great practical value.

Emergency War Surgery. Nato Handbook. Prepared for use by the Medical Services of Nato Nations. (Pp. 411; 18 figures. $2.25.) Washington, D.C.: United States Government Printing Office. 1958.

This important publication will be of great value not only to the Services but to all concerned with training doctors and laymen for civil defence.

Sensorische Aphasien und Amusien auf myeloarchitektonischer Grundlage. By K. Kleist. (Pp. viii + 45; 47 figures. DM 16.80.-.) Stuttgart: Georg Thieme. 1959.

In this book the architecture of the cerebral cortex concerned with the sensory side of speech is considered in detail. Then a few cases of sensory aphasia are considered in which the brain has been studied carefully by serial section.

Medulloblastoma. By Benjamin L. Crue, Jr. (Pp. x + 206; 16 figures. 43*s*) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

One fourth of all brain tumours in children are medulloblastomas. Treatment is of limited value but in the older age groups long periods of survival have been reported. To the author of this monograph this type of tumour is both a challenge and a hobby. He feels that this tumour should throw light on problems of neoplasia in general. With 400 references he has provided a useful collection of information about the subject.

The Central Nervous System and Behaviour. Transactions of the First Conference, 1958. Edited by Mary A. B. Brazier. (Pp. 450; 168 figures. $5.25) New York: Josiah Macy, Jr. Foundation. 1959.

These transactions are of special interest for the authoritative and beautifully illustrated account of the development of Russian neurophysiology.

The present day work described in this field includes the demonstration of conditional reflexes by direct stimulation of the brain.

Minds Matter. A New Approach to Mental Health. By Beryl P. Cooper. (Pp. 62. 2*s*. 6*d*.) London: Published by the Conservative Political Centre on behalf of the Bow Group. 1958.

The Bow Group is a group of younger Conservatives who cooperate in research on political problems. In this pamphlet, the subject is the mental health services, and the author, a former hospital secretary, gives her recommendations. These are:

(i) That certification should be abolished.

(ii) That new hospital buildings should be "day" and "night" hospitals on the lines of the Worthing experiment.

(iii) There should be a decentralization of administration, and hospitals should receive five-year block grants for maintenance rather than the annual grants they receive at present.

In a pamphlet of this nature, there is much that one can agree with and much that would work better in theory than practice; but all in all the author argues her case well, and the book will serve a useful purpose if it stimulates the interest of the public in the problems of mental health.

Psychopathic Personalities, 9th ed. By Professor Kurt Schneider; Translation by M. W. Hamilton, Foreword by E. W. Anderson. (Pp. xiv + 163. 18*s*.) London: Cassell. 1958.

The Department of Psychiatry of the University of Manchester has rendered this country a notable service in making this translation available. Professor Schneider's work is a classic of German psychiatry, and is a standard educational text in many countries. British psychiatry has suffered from the fact that it has not been a text here, so that much of the teaching to which the student is subjected is open to fundamental criticisms. The principal error which the British psychiatrist makes is

to try to identify the concept of psychopathic personality with one or more clinical syndromes.

Schneider himself made a great advance when he brought psychopathic personality into relation with normal variation. In his textbook he clarifies concepts with the aid of this idea, but eventually has to abandon it for descriptive purposes. Only because they are not readily applied in practical work, he finds it necessary to criticise the systematic typologies of Gruhle, Kahn, and others. His general discussion of typologies is most informative and valuable.

In the last part of his book he gives an account of some 10 different varieties of psychopath, with excellent clinical descriptions. It is a pity that from this part of the work the student might derive the idea that these types are anything better than descriptive aids, and that qualitative rather than quantitative differences might be found between them.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books received.)

Die Entfremdungserlebnisse. By Joachim-Ernst Meyer. (Pp. viii + 64. DM 12.60.) Stuttgart: Georg Thieme. 1959.

Surgery in World War II: Neurosurgery, Vol. I. Prepared and published under the direction of Major General S. B. Hays; Editors for **Neurosurgery** R. Glen Spurling and Barnes Woodhall, with the assistance of Elizabeth M. McFetridge. (Pp. xix + 466; 130 figures. $5.00.) Washington, D.C.: Walter Reed Army Medical Center. 1958.

Neuroftalmologia. By P. Ottonello and G. W. Vassura. (Pp. 611; 149 figures. Lira 15,000.) Bologna: L. Cappelli Editore. 1959.

Diagnostic des Lésions Intra-Craniennes par les Radio-Isotopes (Gamma-encéphalographie). By Thérèse Planiol; Foreword by Prof. D. Petit-Dutaillis. (Pp. 258; 153 figures. Fr. fr. 5,000.-.) Paris: Masson et Cie. 1959.

Recent Progress in Psychiatry, Vol. III [*Journal of Mental Science*]. Edited by G. W. T. H. Fleming and A. Walk. (Pp. 397. 42*s*.) London: J. & A. Churchill. 1959.

Symposia on Child and Juvenile Delinquency [presented at the American Orthopsychiatric Association]. Edited by Benjamin Karpman. (Pp. 364 + Index; illustrated. $10.00.) Washington: Station L. 1959.

Mental Illness in London. By Vera Novies. (Pp. 317; 11 figures. 35*s*.) Published for the Institute of Psychiatry by Chapman & Hall, London. 1959.

Les Médicaments du Système Nerveux Cérébro-Spinal. Edited by F. Mercier. (Pp. 573; 25 figures. Fr. Fr. 5,800.-.) Paris: Masson et Cie. 1959.

Ataractic and Hallucinogenic Drugs in Psychiatry. Report of a Study Group [*Wld Hlth Organ. Tech. Rep. Ser.* No. 152]. Pp. 72. 3*s*. 6*d*.) London: H.M.S.O.; Geneva: WHO. 1958.

Pain, 2nd ed. By Harold G. Wolff and Stewart Wolf. (Pp. 121; 20 figures. 32*s*. 6*d*.) Oxford: Blackwell Scientific Publications. 1958.

The Innervation of Muscle: A Biopsy Study. By C. Coërs and A. L. Woolf. (Pp. xv + 149; 281 figures. 42*s*.) Oxford: Blackwell Scientific Publications. 1959.

Curare and Curare-Like Agents [Proceedings of International Symposium, Rio de Janeiro, 1957, under the auspices of UNESCO]. Edited by D. Bovet, F. Bovet-Nitti, and G. B. Marini-Bettòlo. (Pp. xi + 478; heavily illustrated. 85*s*.) London: D. Van Nostrand. 1959.

Nurse-Patient Relationships in Psychiatry, 2nd ed. By Helena Willis Render and M. Olga Weiss. (Pp. vii + 319. 46*s*.) New York—London—Toronto: McGraw Hill Publishing Co. 1959.

Électromyographie dans les Maladies Nerveuses et dans le Cryptotétanie. By N. Rosselle, with the collaboration of K. de Doncker, P. Jolie, and S. Ligot. (Pp. 159; 183 figures. Bel. frs. 200.-.) Louvain: Éditions Nauwelaerts. 1958.

Practical Handbook of Psychiatry for Students and Nurses, 4th ed. By L. Minski. (Pp. 152. 7*s*. 6*d*.) London: Heinemann. 1959.

The Nature of Stress Disorder [Conference of the Society for Psychosomatic Research, May, 1958]. Foreword by J. Hambling; Preface by C. Newman. (Pp. 298; 16 plates, 21 figures. 25*s*.) London: Hutchinson Medical Publications. 1959.

Involutional Melancholia: An etiologic, clinical and social study of endogenous depression in later life, with special reference to genetic factors. By Ake Stenstedt. (Pp. 71.) Copenhagen: Ejnar Munksgaard. 1959.

Dégénérescence Hépato-Lenticulaire. By Georges Boudin and Bernard Pepin; Foreword by Prof. Th. Alajouanine. (Pp. 250; 46 figures, 1 colour plate. Fr. frs. 3,500.-.) Paris: Masson et Cie. 1959.

Geniale Menschen, 5th ed. By Ernst Kretschmer. (Pp. viii + 311. DM 36.-.) Berlin—Gottingen—Heidelberg: Springer Verlag. 1958.

The Effect of Advancing Age upon the Human Spinal Cord. By L. Raymond Morrison, with the collaboration of Stanley Cobb and Walter Bauer. (Pp. x + 127; 90 figures. 48*s*.) Harvard University Press (London: Oxford University Press). 1959.

The Pergamon Institute (English address: Headington Hill Hall, Oxford) announce that English editions of the *Pavlov Journal of Higher Nervous Activity and Problems of Cybernetics* are being prepared. Specimen copies and subscription rates on application.

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SOME OBSERVATIONS ON THE PATHOGENESIS AND NATURAL HISTORY OF INTRACRANIAL ANEURYSMS

BY

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The purpose of this paper is to present an account of the development of intracranial aneurysms and to describe the way in which they grow and rupture. It is hoped that this account and the coloured illustrations which accompany it will be of interest and use to the clinicians and radiologists working in this field who cannot obtain such a good view of the lesions as can the pathologist.

The observations which follow are based on the personal dissection, using a simple dissecting microscope, of 163 ruptured cerebral aneurysms and of some 40 unruptured aneurysms. The photographs have been made by using the macro-attachment for the Vicker's projection photomicrography equipment, with Kodak "ektachrome" as the colour film. The specimens, after careful cleaning under the dissecting microscope, were suspended across a metal ring by threads attached to the arteries and were illuminated by oblique incident beams from below, and the photographs taken at linear magnifications varying between three and eight times. Depth of focus was obtained by cutting down the lens aperture to *f*22 and increasing exposure time accordingly. This method of illumination may give an unpleasant irregular lighting to the background, but this aesthetic blemish is amply repaid by the detailed delineation of the contours of the subject which are obtained.

The aneurysms which form this series have all arisen in close relationship to the angles of branching and anastomosis in, or close to, the circle of Willis. The distribution of the ruptured aneurysms is listed in Table I.

TABLE I

DISTRIBUTION OF RUPTURED ANEURYSMS

Anterior communicating artery	..	46 (28·2%)
Anterior cerebral artery	..	20 (12·3%)
Proximal part	4	
Distal part	16	
Middle cerebral artery	..	54 (33·7%)
Origin	14	
Main division	34	
Distal	6	
Internal carotid at posterior communicating artery	..	30 (18·4%)
Right side	24	
Left side	6	
Basilar artery	..	7 (4·3%)
Posterior cerebral artery	..	3
Vertebral artery	..	1
Posterior inferior cerebellar artery	..	1
Left anterior choroidal artery	..	1
		163

In 20 instances (12·3% of the cases) a second unruptured aneurysm was present. Only with aneurysms arising in the angle between the posterior communicating artery and the internal carotid artery, which were four times more common on the right than on the left side, was any significant difference between the two sides found.

Natural History of the Aneurysms

The aneurysms originate from one of the junctional angles in which the circle of Willis and adjacent vessels abound (Fig. 1). They are multiple in one eighth of the cases and when this occurs the common descriptive term, "berry aneurysm", is particularly appropriate (Fig. 2). In the case of the anterior communicating artery, which is often only 2 or 3 mm. long, the aneurysm often involves the whole length of the artery (Fig. 3), though it may be more clearly arising at one end. Once started, the aneurysm tends to enlarge slowly but relentlessly: as it grows it commonly becomes irregular in shape, perhaps wrapping itself around adjacent vessels and nerves (Fig. 4), and in this way an aneurysm with quite a narrow neck may appear to have a broad origin from its parent vessel. As the aneurysms grow they often become bilocular (Fig. 5), but even those which remain grossly spherical or ovoid may show on closer scrutiny an appearance as of bubbles erupting from the surface (Fig. 6). It is evident that these "bubbles" are extremely thin-walled.

It is usually when the aneurysms have attained a diameter between 6 and 15 mm. that clinical effects are produced, though it must be emphasized that many aneurysms never produce effects at all, while a few attain a much greater size and simulate tumours (Fig. 7). The one thing which may check the progressive enlargement of an aneurysm is the occurrence of extensive thrombosis within it (Fig. 8),

and when this happens the aneurysm may appear much smaller in an arteriogram than it turns out to be at a subsequent operation or necropsy, or it may completely fail to fill.

Microscopic examination of the neck of an aneurysm (Fig. 8) shows that the muscle coat of the artery ceases abruptly at the point of origin, but the elastic lamina may sometimes extend some little distance into the body. At the fundus the wall comprises only an attenuated layer of hyaline fibrous tissue which merges imperceptibly with the imperfectly organized thrombus in the cavity, and on the outside fuses with the meninges or with any other anatomical structure on which it may impinge.

Leakage and Rupture of Aneurysms

There is probably no useful purpose to be served in attempting to distinguish between the leaking or "weeping" of a berry aneurysm and its frank rupture. Microscopic examination of the thinned-out fundus of an aneurysm sometimes shows a thin smear of fibrin with a few entangled blood cells on the outside, the appearance suggesting permeation of these elements through the wall: but in practice, if an aneurysm has bled significantly then a rupture is present, though this may vary from a minute pin-hole to disruption of the whole aneurysm, with parallel variation in the clinical features.

Aneurysms usually rupture when they have reached a diameter of 6 to 15 mm. but occasionally they burst when they are quite minute. When this happens, the appearance may be almost as if the hole had developed directly in the artery (Fig. 9) and the clinical course is likely to be of a fulminating character.

The 163 ruptured aneurysms listed in Table I have been carefully studied to determine the precise part of the aneurysmal sac at which rupture has occurred. Dividing the wall between the fundal pole and the neck into equal thirds, the rupture was classified as fundal if it occurred in the distal third, lateral in the middle third, and cervical in the proximal third; while, if for some reason, such as obscuring of the original state by operative procedures or damage at necropsy, the location of the rupture could not be confidently stated, the site of rupture was put down as undetermined. The findings are given in Table II and it will be seen that at least 64% of all aneurysms and 105 (84%) out of 125 for which the site could be determined, ruptured at the fundus.

TABLE II

SITE OF RUPTURE FOR 163 CEREBRAL ANEURYSMS

Site of Rupture	No. of Aneurysms
Fundal segment	105 (64%)
Lateral segment	17 (10%)
Cervical segment	3 (2%)
Undetermined	38 (24%)

A typical example of fundal rupture is illustrated in Fig. 10, while Fig. 11 shows a lateral rupture and Fig. 12 the only cervical rupture which it has proved possible to photograph. (There is technical difficulty in mounting for photography aneurysms which rupture at the neck, as the tear tends to extend and the aneurysm separates from its parent vessel.) Sometimes recurring episodes of haemorrhage and thrombosis occur at a single point of rupture. This results in a craggy, ulcer-like lesion with everted edges formed of successive layers of blood clot, while the neighbouring tissues acquire the characteristic golden colour of haemosiderin (Fig. 13).

The importance of the above observation on the frequency of fundal, as opposed to lateral and cervical rupture, lies in its application to surgical treatment. With present techniques, the most satisfying surgical procedure for ruptured aneurysm is the placing of a clip across the neck (Fig. 14) and this can clearly apply only when the rupture is distally situated. It may, therefore, be reassuring to the neurosurgeon to learn that there is a high probability—approximately three chances in four—of any aneurysm he approaches having its rupture at the fundus, and only a small possibility—of the order of one in 30—of the tear being at the neck.

Serial sectioning of ruptured aneurysms reveals that the rupture often occurs by the bursting of one of the bubbles referred to above (Figs. 2, 4, and 6), but in aneurysms which contain considerable amounts of thrombus, the break is effected by blood dissecting up between the thrombus and the wall until it reaches the fundus, where these structures merge in ill-defined degenerate collagen-like layers, through which the burst takes place.

Pathogenesis

The microscopic anatomy of the cerebral arteries reveals two features which render these arteries particularly prone to aneurysm formation: first the media, in which the main strength of an artery resides, is much thinner than in other vessels (such as coronary arteries) of comparable calibre; and second, although there is a well developed internal elastic lamina, the external elastic lamina is very poorly developed and may be altogether absent. Add to this the fact, first clearly emphasized by Forbus (1930), that developmental faults in the media, leaving gaps of varying size, occur quite commonly at the points of arterial junctions, and the heavy responsibility thrown on the internal elastic lamina for maintaining the arterial wall will be appreciated. The occurrence of these medial faults has now been fully confirmed (Glynn, 1940)

FIG. 1.—Typical berry aneurysm arising in the angle between the middle cerebral artery and a large branch. Large lipoid atheromatous plaques are present at the neck of the aneurysm and at the origin of the adjacent branch where there is some degree of dilatation.

FIG. 2.—Two aneurysms arising at branches of a middle cerebral artery.

FIG. 3.—Aneurysm arising from the whole length of the anterior communicating artery. A second small communicating vessel joins the two anterior cerebral arteries just distal to the aneurysm.

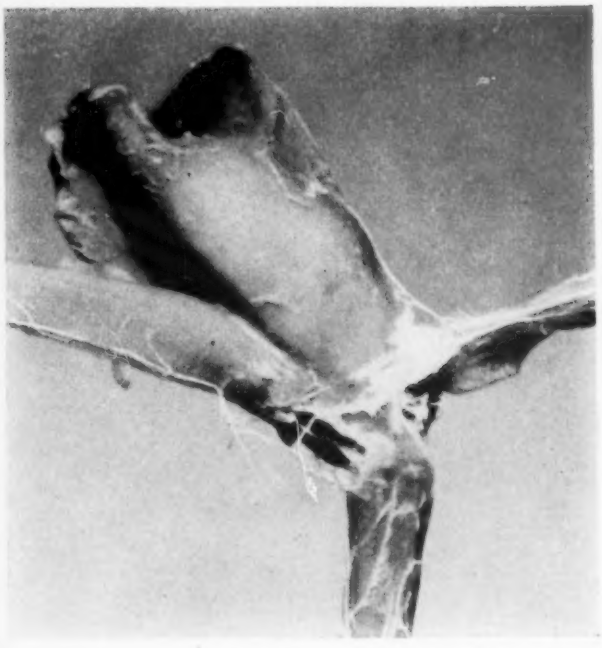

FIG. 4.—Middle cerebral artery aneurysm which had wrapped itself around the afferent trunk, giving a false impression of a broad origin. It has been partially dissected free. This aneurysm also shows a ruptured "bubble" at the fundus.

FIG. 5

FIG. 6

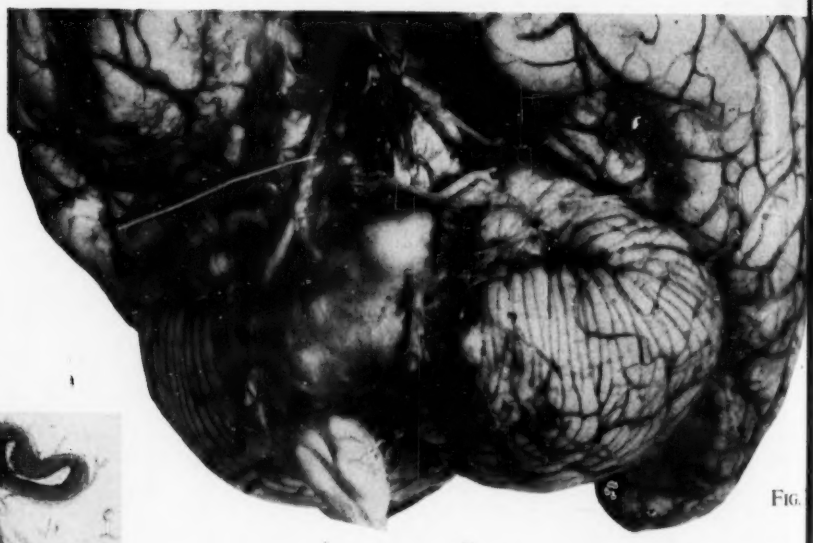

FIG.

FIG. 8

FIG. 5.—Bilocular aneurysm of the internal carotid artery at the origin of the posterior communicating artery. The larger loculus has ruptured at its fundus. Atherosclerotic lesions are conspicuous.

FIG. 6.—Middle cerebral artery aneurysm showing bubble-like formations. It has ruptured through a small "bubble" at the fundus.

FIG. 7.—Large unruptured aneurysm of the left vertebral artery, causing fatal compression of the brain-stem.

FIG. 8.—Longitudinal section through the middle cerebral artery at the point of origin of an aneurysm. The fundus of the aneurysm contains much imperfectly organized thrombus. The muscle coat of the artery ceases abruptly at the neck of the aneurysm, but the elastic tissue (darkly stained) extends a short distance into the wall of the sac.
Weigert's elastic stain, ×16.

FIG. 9

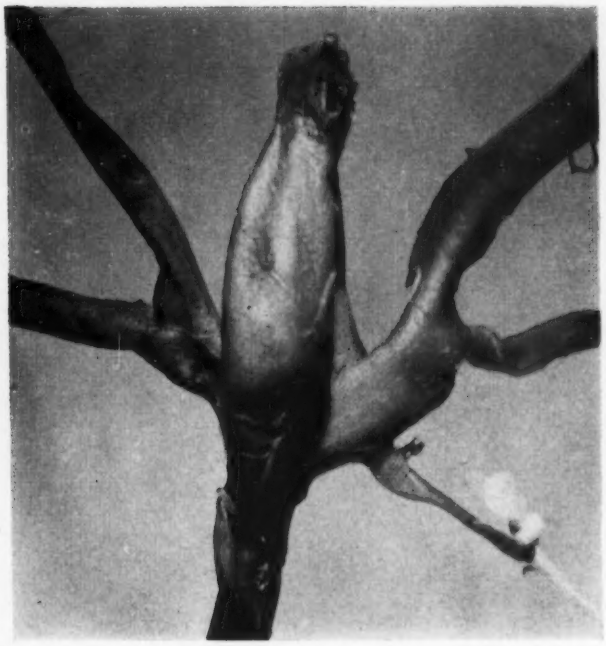

FIG. 10

FIG. 11

FIG. 12

FIG. 9.—Rupture of a minute aneurysm of the anterior communicating artery. The proximal part of the left artery is hypoplastic.

FIG. 10.—Typical example of an aneurysm at the first main bifurcation of the middle cerebral artery which has ruptured at the fundus.

FIG. 11.—Aneurysm at the bifurcation of the basilar artery, showing large lateral rupture.

FIG. 12.—Aneurysm of the middle cerebral artery which has ruptured at the neck.

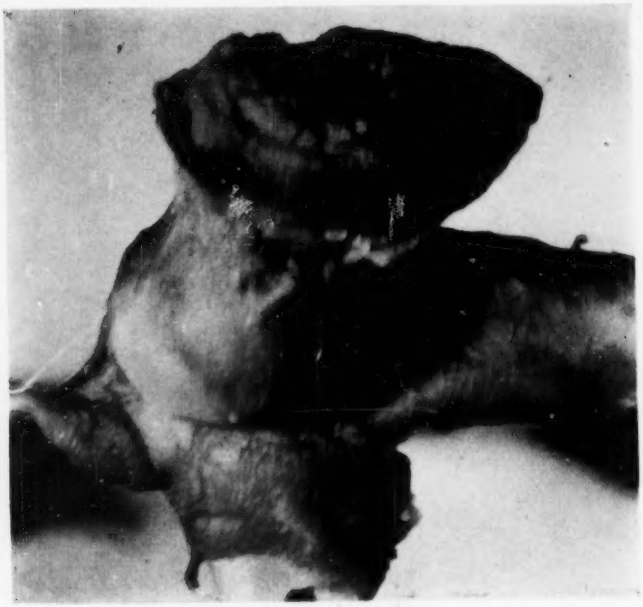

FIG. 13

FIG. 14

FIG. 15

FIG. 16

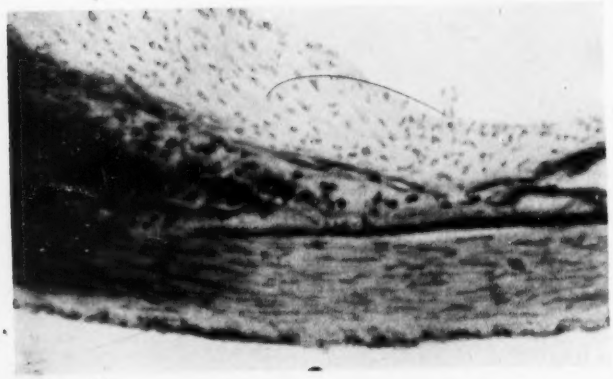

FIG. 17

FIG. 13.—Internal carotid artery aneurysm which has been the site of repeated haemorrhages through a fundal rupture. Thrombus is erupting through the burst and haemosiderin pigmentation is present in the adventitia of the adjacent vessels.

FIG. 14.—Aneurysm on the basilar artery at the origin of the superior cerebellar artery. The aneurysm has ruptured at the fundus and the neurosurgeon has placed a clip across the neck.

FIG. 15.—Longitudinal section through bifurcation of the middle cerebral artery showing a minute medial defect at the apex of the fork. Weigert's elastic stain, ×18.

FIG. 16.—Similar section to the previous figure, but showing a very much larger medial fault. The intima is thickened at the site of the medial lesion. Weigert's elastic stain, ×25.

FIG. 17.—Frozen section showing the edge of an atheromatous plaque in the basilar artery. The internal elastic lamina is infiltrated with fat and is quite lost in the substance of the plaque. Haematoxylin and sudan IV ×40.

and indeed their frequency has proved an embarrassment to those who would maintain that they are the essential causative lesions of the aneurysms. The faults, however, vary greatly in size, from tiny discontinuities of the muscle near the apex of the fork (Fig. 15) up to gaps of several millimetres in length (Fig. 16).

Two other factors come up for consideration in the production of these aneurysms, the blood pressure and atheromatous lesions in the vessels. The blood pressure is the distending force concerned and it must be clear that the normal blood pressure of early life may fail to produce an aneurysm through a small fault in the vessel wall, but succeed in doing this through a large one: and conversely, a small fault may resist distention by the normal blood pressure of early life, but yield before the higher blood pressures of middle age or before pathological hypertensive pressures.

Atherosclerosis is the remaining factor and its role has been stressed by Carmichael (1950) and by Walker and Allegre (1954). It is customary to emphasize the intimal lesion of atherosclerosis, and the medial changes which are a constant feature (Crawford and Levene, 1953) are often overlooked. These changes consist of localized medial thinning, down to almost complete disappearance in some cases, and in the cerebral arteries there is often extensive infiltration of the media with fat (Carmichael, 1950). More important in the present connexions, the internal elastic lamina also often degenerates at the base of an atheromatous plaque (Fig. 17). When the atheroma occurs at a site already weakened by a developmental fault, then the effect is likely to be additive and loss of the internal elastic lamina (the only significant source of strength at these points) may well result in aneurysmal dilatation. It is well known that severe atherosclerosis may be the sole pathogenetic factor in aneurysms of the abdominal aorta. The same may be true of fusiform aneurysms of the basilar artery (Fig. 18), and it is no surprise to find milder degrees of atheroma contributing to the pathogenesis of the commoner berry aneurysms. Evidence of a statistical character for the association between berry aneurysms and atherosclerosis is presented in Table III. In this table the frequency of severe coronary atheroma and its effects in the males aged 45 to 70 from the present series of deaths from ruptured cerebral aneurysm is compared with the frequencies in men of the same age dying of causes not directly related to vascular disease. It will be seen that all the criteria of severe coronary atherosclerosis employed are from two to three times more frequent among victims of ruptured cerebral aneurysm than in the control group. (The control figures in Table III have been kindly provided by the Social Medicine Research Unit of the Medical Research Council from their national survey of necropsies in this age group (Morris and Crawford, 1958)).

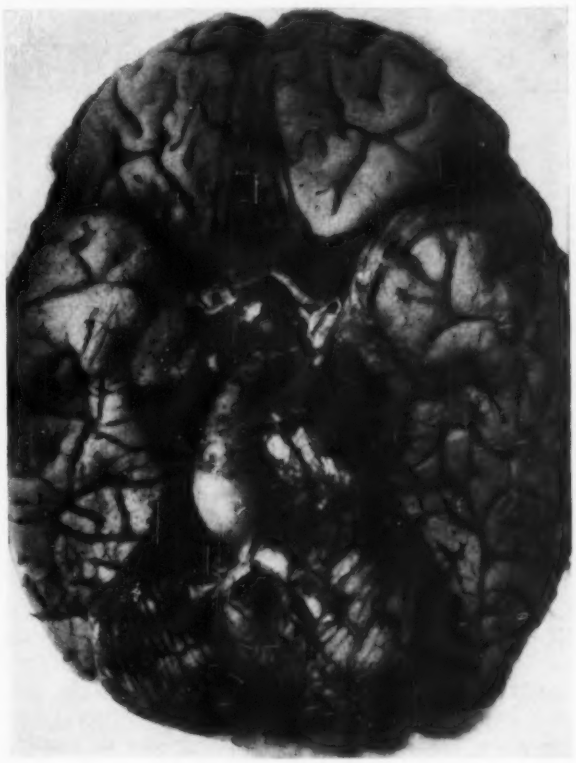

FIG. 18.—Atheromatous fusiform aneurysm of the basilar artery.

An attempt to indicate the inter-relationships between the three pathogenetic factors in cerebral aneurysms occurring at different ages is made in Table IV. In this table the numbers are not intended to have precise mathematical significance, but to imply degrees for the various factors: thus, under

TABLE III

CORONARY ARTERY DISEASE IN MEN AGED 45 TO 70 YEARS DYING FROM RUPTURED CEREBRAL ANEURYSM

	Total Cases	Severe Coronary Atheroma	Severe Coronary Stenosis	Coronary Calcification Present	Small Myocardial Scars	Large Myocardial Scars
Deaths from primary ruptured cerebral aneurysm	49	44%	16%	28%	12%	4%
Control deaths unrelated to vascular disease	2,785	15%	3%	18%	5·2%	1·8%

TABLE IV

RELATIVE IMPORTANCE OF PATHOGENETIC FACTORS IN CEREBRAL ANEURYSMS AT DIFFERENT AGES

Age Group	Pathogenetic Factor		
	Medial Defect	Blood Pressure	Atherosclerosis
Childhood and adolescence	4*	1	0
Early adult life	3 - 2	1 - 3	0 - 2
Middle age	2 - 1	2 - 4	1 - 3
Old age	1 - 0	2 - 4	2 - 4

* For explanation see text.

the heading of medial defect, 0 indicates absence, 1 a trivial fault and 4 the largest faults; similarly 0 to 4 indicate absence of and degrees of severity of atherosclerosis, while under blood pressure, 1 and 2 imply physiological blood pressures of early and later life, while 3 and 4 indicate moderate and severe hypertension.

The extremes are represented by the aneurysms of childhood, when a large defect yields before the low normal blood pressure of that age and by the aneurysm of the elderly hypertensive atherosclerotic subject in which a medial defect plays no part, though the latter is likely to be of the fusiform rather than of the berry type. At intermediate ages all the factors are likely to be concerned in varying degrees.

Summary

A study of 163 ruptured berry aneurysms of the cerebral arteries is presented and the different types illustrated. The site of rupture is in the fundal segment in at least 64%, while cervical rupture is uncommon. Pathogenesis is discussed: the three main factors—developmental faults in the media, atherosclerosis, and hypertension—play roles of varying importance according to the age at which the aneurysm develops.

I wish to thank Dr. Margaret D. Crawford of the M.R.C. Social Medicine Research Unit, The London Hospital, for drawing up Table III, and Professor J. N. Morris, Director of the Unit, for permission to use the control figures in that table.

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REFERENCES

Carmichael, R. (1950). *J. Path. Bact.*, **62**, 1.
Crawford, T., and Levene, C. I. (1953). Ibid. **66**, 19.
Forbus, W. D. (1930). *Bull. Johns Hopk. Hosp.*, **47**, 239.
Glynn, L. E. (1940). *J. Path. Bact.*, **51**, 213.
Morris, J. N., and Crawford, M. D. (1958). *Brit. med. J.*, **2**, 1485.
Walker, A. E., and Allegre, G. W. (1954). *J. Neuropath. exp. Neurol.*, **13**, 248.

J Neurol. Neurosurg. Psychiat., 1959, **22**, 267

SOME SENSORY SYNDROMES IN CHILDREN : INDIFFERENCE TO PAIN AND SENSORY NEUROPATHY

BY

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It is the purpose of this paper to direct attention to several curious and infrequently encountered conditions which may present in infancy or early childhood with a similar clinical picture. Failure to react normally to painful or noxious stimuli is the outstanding feature, and this abnormality is usually first recognized when the patient is undisturbed by an injury which obviously should be painful. As most of these conditions bear a superficial resemblance to one another we suggest employing the general term "sensory syndrome" to describe them, and have been fortunate in being able to examine five examples. By reporting illustrative cases we propose to bring forward evidence indicating that several pathological conditions are included in this clinical picture.

Congenital Indifference to Pain

In the first condition, congenital indifference to pain, there is no objective neurological abnormality except that the patient, although recognizing the nature of all types of stimuli at normal thresholds, fails to evince the usual clinical manifestations associated with accepted pain-producing stimulation.

Case 1. (A.C., NH 32034).—This patient is a 14-year-old girl.

Family History.—The parents are first cousins, the patient's grandmothers being sisters. There is no known neurological disease in either family. The parents and only sibling have been examined and no abnormality detected. There is no left handedness in the family.

Medical and Developmental History.—The patient was born at full term after an uneventful pregnancy and delivery. She developed normally during her first year, walked, and said a few words by her fourteenth month. When she was aged 10 months her parents noticed that she was inclined to chew her tongue, causing large ulcers which appeared to be painless and which eventually led to the destruction of the tip of the tongue. She was unsteady on her feet until the age of 3 years and never cried although she had many falls and sustained numerous minor injuries. When she was 2½ years old handfuls of her hair were pulled out by a playmate; at 3 she smashed her fingers in a door; at 4 she sustained a severe laceration of the forehead. In each of these injuries she exhibited no evidence of pain, and indeed, on several occasions her injury was unsuspected until noticed by her parents. At the age of 6 years her right hip became swollen over a period of two weeks. This was associated initially with a limp, which increased till eventually she complained of being unable to move the leg. Three weeks from the onset she was admitted to hospital, where a fracture of the right femur was diagnosed. At no time during this period, even while walking, did she complain of pain. At the age of 10 years she fell while playing and noticed on getting up that her wrist "bent the wrong way". She had sustained a painless compound fracture of the left wrist, which was set without anaesthesia and without causing her any discomfort.

In the three years since her last admission to the National Hospital the patient has matured considerably and has made a better adjustment to her disability. She is now careful to avoid injury and is generally successful although she occasionally finds blisters on her fingers from burns of which she has been unaware. She cannot recall having had a headache, earache, stomach ache, colic, or having experienced pain. She experiences hunger and thirst, sweats readily, and on exposure to cold has goose flesh. Her teeth are extremely carious but cause her no discomfort. She realizes when she has a foreign body in her eye but is not distressed by it.

Examination.—She is a right-handed girl whose I.Q. on the Terman-Merrill scale is 126. Her face is wizened, causing her to look older than her stated age. Psychiatric examination does not elicit anything suggestive of a hysterical reaction. General examination is not remarkable except for the multiplicity of scars on the tongue, elbows, hands, knees, feet, and buttocks. The right femur is slightly shorter than the left and she has a hydroarthrosis of the right knee joint (Fig. 1). Both her ankle joints are deformed by bony overgrowth. She is unable to detect the odours of asafoetida, coffee, tobacco, or lavender, nor can she taste sugar, salt, quinine, or tartaric acid. It is possible that her loss of taste may be related to the extensive scarring of the tongue. There is no wasting or other abnormality of development, power,

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FIG. 1.—Multiple scars of both knees and bony deformity of the right knee joint.

tone, or coordination of the muscles of the extremities. Her gait is normal. The tendon reflexes are present and symmetrical, and the plantar responses are flexor. The corneal reflexes can be elicited, but are less brisk than normal. Light touch and tickling with a wisp of cotton, small ranges of movement at joints, vibration and discrimination between one and two closely placed points of contact on the finger tips are all normally perceived. She is able to detect small differences in the temperature of an object placed against her skin, and to distinguish easily between the sharp and blunt ends of a pin. Recognition of the nature of objects placed in her hands when her eyes are closed is good. Her sensory threshold has been examined, using as a stimulus a square wave electrical pulse of 1 millisecond's duration and variable strength provided by a constant voltage stimulator (Walter and Ritchie, 1945). This is normal everywhere, except distal to the knees where it is slightly elevated. This elevation may be the sequel to the trauma to which the legs have been subjected. The reactions usually associated with pain have not been produced even with the strongest of stimuli. Stimulation with up to 100 volts is intolerably painful to the examiner, but causes her no discomfort although it occasions violent muscular contraction. If a blood pressure cuff is inflated on her arm to 220 mm. Hg she is able to make a fist 130 times in two minutes without discomfort; on the other hand, in a healthy subject severe pain usually develops after 40 to 60 contractions. Immersing her hand in water at temperatures of 1° C. and 65° C. causes no pain and she does not object to deep pressure on the tendo Achillis. Intravenous injection of 0·25 mg. of histamine causes a bad taste in her mouth and throbbing in her head but no headache (Clark, Hough, and Wolff, 1936). Pressure on the eyeball causes the cardiac rate to drop from 96 to 84 per minute but no expression of pain. Scratching the neck results in no painful sensation but produces a change in pupil size. The cutaneous axone reflexes, tested by scratching the skin with a pin and by the intradermal injection of histamine, are normal. When liberally dusted with "itching powder" there is the usual erythematous reaction which is not, however, associated with an itching sensation. The patient's refusal to be exposed to radiant heat has prevented detailed testing of her sweating reaction. She has been observed during examination to be perspiring about the face, in the axillae, and on the palms of the hands and soles of the feet. No thickening of peripheral nerves has been noted on palpation.

Radiological studies at the age of 7 years showed an old healed fracture of the upper part of the shaft of the right femur with marked angulation of the neck. There were osteochondritic changes involving the right knee joint and avascular necrosis of the epiphysis of the left os calcis and right astragalus. These changes were accepted as traumatic in origin. Air encephalography revealed no defect of the cisterns or of the ventricular system. Dr. Hallpike found normal cochlear and vestibular functions. Electro-encephalography undertaken by Dr. Cobb showed no abnormality; the alpha rhythm blocked normally with eye opening and sudden noises. Dr. Dawson has kindly allowed us to report that he obtained through the intact scalp good evoked potentials from the cortical sensorimotor area on electrical stimulation of the ulnar nerve. The Wassermann reactions in the blood and cerebrospinal fluid were negative. The fluid contained no increase in cells or in protein. On two occasions a portion of an interdigital nerve with the overlying skin was excised from the foot and examined histologically

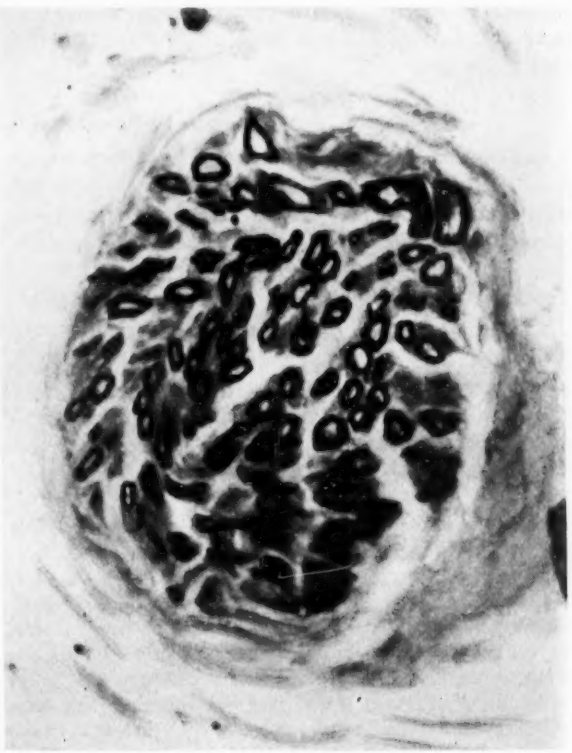

FIG. 2.—Interdigital nerve of left foot. The appearance is that of a normal nerve. (Osmic acid stain × 300.)

sing a number of stains including osmic acid and methylene blue (Fig. 2). Professor Blackwood detected no abnormality of the peripheral nerves and observed many small nerve fibres in the superficial dermis. These accompanied capillaries or passed toward the basal epidermis.

To sum up, this is an intelligent girl in whom the motor system appears to be functioning normally and who reports normal responses dependent on the integrity of the peripheral autonomic nervous system. On the sensory side it has not been possible to evoke the normal reactions commonly associated with the experience of pain when a variety of stimuli have been used. The stimuli have been those accepted as producing pain, such as multiple heavy pinprick, heavy pressure on tendons, and extremes of cold and heat. Pain from structures within the head, such as may be provoked by intravenous histamine in healthy subjects, has not occurred.

Tests have shown that the peripheral and central pathways necessary for the recognition of various forms of stimulation are intact. The cardiac and pupillary responses to pressure on the eyeball and scratching the neck and the flare of the triple response of Lewis, dependent on the integrity of the peripheral sensory nerve fibres, are normal. Added information to show that the peripheral pathway is normal has been obtained by the study of suitably stained sensory nerves and skin. Further, no gross deformity of the brain has been found by air encephalography. It would therefore appear that the peripheral sensory pathway is intact, that following peripheral stimulation impulses reach those parts of the brain requisite for the recognition of the method of stimulation, but that there is an absence of the appreciation of pain. The nature of the mechanism at fault remains unknown. It is possible that it may result from some congenital anomaly of an undetermined order.

It is of interest that this patient in her early years became progressively more deformed by repeated self-inflicted injury as is usually the case with such patients (Murray, 1957; Petrie, 1953) Although her reaction deficit has remained unchanged, she has managed in recent years to avoid serious injury. This subjective improvement in her status is most probably the result of more intelligent self-management (McMurray, 1950).

The first documented description of this condition, which has been called "congenital indifference to pain", appeared under the title "A case of congenital general anaesthesia" (Dearborn, 1932). This was the now famous case of Edward H. Gibson, who achieved a degree of notoriety in vaudeville circles as "the human pincushion", allowing members of the audience to push pins into his tissues. He was a man of normal intelligence without neurological abnormality other than indifference to pain which had been present since childhood. Since 1931 over 40 cases have been referred to in the literature, most of which have been reviewed by Fanconi and Ferrazzini (1957). Critchley (1956) has quite properly pointed out that many of these cases have been inadequately studied. In some instances either the patient's intelligence has not been taken into consideration or the presence of a sensory neuropathy has not been excluded.

The significance in our case of anosmia and ageusia is difficult to assess. These defects have been reported in association with cases diagnosed as congenital indifference to pain (Roe and Leys, 1950; Madonick, 1954; Grain and von Hagen in Boyd and Nie, 1949), and will be discussed in greater detail below.

We wish to stress that the term "congenital indifference to pain" should be applied only to those patients who, perceiving correctly the nature of stimuli at normal thresholds, fail to react in the usual defensive manner with withdrawal of the offended part, acceleration of pulse and respiration, and elevation of blood pressure (Nafe and Wagoner, 1938; Wolf and Hardy, 1941) as in a healthy subject. Patients given this diagnostic label should not be mentally deficient, and should have normal deep tendon and cutaneous axone reflexes and normally innervated skin on histological examination. Further, the defective reaction to pain-producing stimuli should have been present from infancy.

Progressive Sensory Radicular Neuropathy

Denny-Brown (1951) applied the term "hereditary sensory radicular neuropathy" to a familial disease formerly called "hereditary perforating ulcer" (Hicks, 1922) or "acropathie ulceromutilante familiale" (Thévenard, 1942 ,1953). This is a familial, progressive, peripheral sensory neuropathy usually involving the feet first and more than the hands, with the sensory level rarely extending above the elbows or knees. The loss of pain appreciation is much more marked than that of the other modalities.

The following case is similar to the cases described by Denny-Brown (1951), but we have applied the term "progressive sensory radicular neuropathy". It is felt, however, that though there is no familial history this patient may be an isolated instance of the hereditary form of the disease.

Case 2 (R.B., NH 58889).—This is a 10-year-old boy.

Family History.—This boy's parents are first cousins, the paternal grandmother and maternal grandfather being siblings. There is no known neurological disease in either family. There is no left handedness in the family and the patient has no siblings.

FIG. 3.—Deformity of ankles.

Medical and Developmental History.—The patient was born at full term after an uneventful pregnancy and delivery. He breathed spontaneously and appeared to be normal. He gained weight at the usual rate but did not hold up his head until the age of 6 months, sat up at 12 months, stood unassisted at 18 months, and walked at 24 months. He was continent of urine and faeces by the age of 3 years with occasional nocturnal enuresis until the age of 7 years. He was speaking words at the age of 2½ years and short sentences at 3 years.

When the patient was 9 months old his parents noticed that he was very clumsy in reaching for objects and did not hold things in his hands. At the age of 12 months he fell against a hot stove, sustaining a severe burn of the right hand. He neither cried nor showed any sign of distress, even though he received a third degree burn which resulted in flexion contractures of the fingers. At the age of 2 years he developed a chronic draining sinus of the left ankle, which did not heal until a fragment of bone was extruded some two years later. There has been intermittent draining since, and considerably bony deformity has developed. At the age of 4 years he became aware of his parents' interest in his unusual disability and would attract attention by placing his hand on the hot stove saying, "No hurt Bobby". When 7 years old he was admitted to the National Hospital. At that time all modalities of sensation except appreciation of temperature were severely impaired below the knees and elbows, while there was no deficit over the trunk; crude differences of temperature were recognized by him in his hands and feet. Motor power in the limbs and trunk was good. Over the years the patient has had innumerable infections of the fingers, which eventually led to the destruction of all the terminal phalanges. He has had many operative procedures without anaesthesia or discomfort. His bladder and bowel function was normal and he has experienced hunger, thirst, and headache.

Examination.—The patient is a right-handed boy with an I.Q. on the Terman-Merrill scale of 85 to 90. The hands and left ankle are deformed (Fig. 3). The terminal phalanges of the fingers have been replaced by scar tissue or granulating wounds, and the left ankle is swollen with a small draining sinus over the lateral malleolus.

The function of the cranial nerves is normal in all respects. He is able to taste and smell. There is neither weakness nor wasting of muscles in the extremities, and coordination is good. With the exception of the triceps reflexes, which are brisk, the tendon reflexes are absent. In the limbs there is a diminution of all sensory modalities including the recognition of temperature which increases distally. The latter modality is completely absent in the left hand and both feet. The pattern of sensory loss is not perfectly symmetrical, for perception of extremes of temperature is present in the palm of the right hand, but not below the wrist of the left hand. Again, in the antecubital fossae the threshold for differentiating hot and cold is about 10° C. on the right and nearly 15° C. on the left. Sense of passive movement is absent at the joints of the fingers and toes. Pinprick, light touch, and vibration are not appreciated below the knees and elbows. As indicated on the sensory chart there is no impairment of sensation over the trunk (Fig. 4). An electrical stimulus of 100 volts is not felt below the wrists or knees while over the arms and thighs the threshold is about 50 volts; over the trunk it is the normal 15 to 20 volts. Pain develops after 40 contractions of the fist with a blood pressure cuff on that arm inflated to 220 mm. Hg. It is interesting that although the onset of the pain is within the normal "time-contraction" period the pain is not felt in the contracting muscles as is usually the case, but under the cuff. Itching and erythema may be produced by itching powder on the trunk but not on the extremities. The cutaneous axone reflexes, elicited with intradermal histamine, are readily obtainable over the trunk, are diminished over the upper part of all four limbs, and absent below the elbows and knees. Sweating occurs over the hands and feet, as elsewhere on the face and trunk. The peripheral nerves are not thickened.

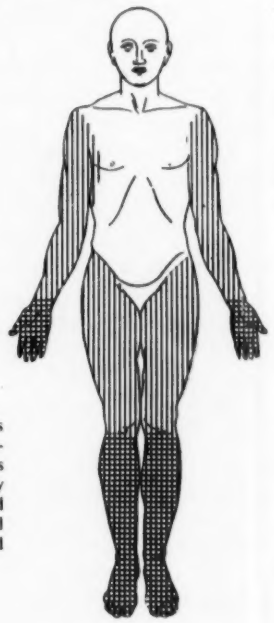

FIG. 4.—The crosshatched areas indicate complete or nearly complete absence of all modalities of sensation. The vertically lined areas indicate a threshold markedly raised to pain and moderately raised to touch and temperature.

FIG. 5.—Interdigital nerve of left foot. Note the great diminution in number of myelinated fibres. (Osmic acid stain × 300.)

Radiological examination (age 8 years) shows disintegration of the left ankle joint with partial absorption of the astragalus and moulding of the os calcis, partial degeneration of the interphalangeal joint, and absorption of the terminal phalanx of the right great toe, and absorption of the terminal phalanges of all the fingers. Dr. Hallpike reports normal cochlear function with severe bilateral reduction of caloric vestibular responses. Dr. Cobb reports no abnormality in the electroencephalogram. The alpha rhythm is well developed and is little affected by eye opening. Examination of the blood and cerebrospinal fluid, including the Wassermann reaction, shows no abnormality.

Histological examination of an interdigital nerve by Professor Blackwood showed several nerve bundles containing shrunken endoneural tubes. Only a few myelinated fibres could be found in the osmic acid sections (Fig.5). These findings are interpreted as being indicative of nerve degeneration.

To sum up, this is a 10-year-old boy with a progressive peripheral sensory neuropathy which probably has been present since early infancy. The sensory signs, though increasing in severity, have remained localized to the periphery of the four limbs. Associated with this sensory deficit there is a loss of axone reflexes in the analgesic areas pointing to a degeneration of the peripheral sensory neurones. Further, the histological studies confirm the diagnosis of degeneration of the peripheral sensory neurone. On the other hand, the complete absence of any evidence of disturbance of motor function clearly indicates that the lesion involves only sensory neurones. As the peripheral autonomic motor functions are also normal, it is difficult to place the lesion anywhere except in the region of the posterior root ganglia where neither motor fibres nor autonomic fibres can be involved. This case suggests hereditary sensory radicular neuropathy because the trunk and bladder are completely spared and the disease has been slowly progressive, involving the feet more than the hands. The extremely early age of onset is unusual in the hereditary disease although several cases have been recorded (Heller and Robb, 1955). Our patient's disease is not familial, but since his parents are consanguineous it may represent the expression of a recessive trait.

Non-progressive Sensory Radicular Neuropathy

We propose to present a second case, contrasting with the previous one in that it is not progressive and the involvement is much more extensive.

This case was presented to the section of neurology of the Royal Society of Medicine on November 2, 1950, by Drs. Lorber and Carmichael. It is unfortunate that in two recent publications it has been referred to as one of congenital indifference to pain (Jewsbury, 1951; Fanconi and Ferrazzini, 1957), for it differs radically from the first case which we report in this paper.

Case 3 (R.M., NH 24347).—This is an 11-year-old boy.

Family History.—There is no known consanguinity or history of neruological disease in either parent's family. The parents and siblings (one brother aged 12 and two sisters aged 6 and 12 when examined) were seen in 1954 and at that time showed no neurological abnormalities. One sister is left-handed.

Developmental and Medical History.—The patient was delivered at full term without instruments after an uneventful pregnancy and 24 hours' labour. He was a breech presentation and was said to have been "completely floppy" and without movement during the first few days of life. He was never cyanotic, but required tube feeding initially and had to be fed with an eyedropper until 7 months of age because of difficulty in sucking. He did not sit up without support until 18 months or stand until 4 years: he walked at 4½ years, but has always been unsteady with a tendency to fall, which has occasioned him many injuries. He began saying single words at 18 months, but it was not until the age of 4 years that he spoke short sentences. He was not continent of urine and faeces until the age of 6 years. At the age of 7 months he scratched his right eye causing a corneal ulceration. Surgery was necessary to preserve his sight. At this time it was first realized that he did not react normally to

painful stimuli. At 9 months he developed a severe gastro-enteritis, which was not associated with any evidence of cramping or colic, and was followed by pneumonia. Severely ill, he was placed in an oxygen tent. His prolonged debilitation following this illness may have contributed to the retardation of his general development. As the patient grew older it became apparent that he had a marked susceptibility to infection. Many minor lacerations and burns became infected, and at one time or another he had whitlows, then osteomyelitis of each of the fingers. These infections led to the absorption of all terminal phalanges, leaving his fingers deformed and almost useless. He had many lacerations about the face, including fracture of the nasal bone, but never experienced pain with any of these injuries and infections. At the age of 9 years he was noted to be looking ill one day, although he denied feeling poorly. His temperature was 103° F. and when he was put to bed it was noted that his left leg was swollen and red from the groin to the ankle. X-ray examination at hospital revealed an unsuspected fracture of the patella. When questioned he denied having pain in the knee and could not recall any immediate injury. When his leg was enclosed in plaster and he was confined to bed he promptly developed bed-sores over the buttocks and thigh, which did not respond to treatment until he was allowed to walk about. Throughout his life this boy has had many minor surgical procedures such as partial finger amputations and nerve biopsies without the administration of anaesthetics, yet without the slightest sign of discomfort.

At the age of 1 year the patient, in association with a fever, had a grand mal convulsion. Following this and until the age of 4 years he had about one typical petit mal seizure weekly; thereafter he has had no minor seizures and only very rare major attacks, for which he is taking "mysoline".

Examination.—This patient has been admitted to the National Hospital on six occasions in the past eight years. That there has been no change in his neurological status or progression of the sensory deficit during this time is well documented. His I.Q. has been repeatedly estimated at from 80 to 88 on the Wechsler children's scale (dull normal range). His countenance is rather that of a retired pugilist, for he looks much older than his years. His nose is flattened, and his mouth deformed by scars. There are innumerable scars over his hands, arms, legs, and buttocks. His fingers are stumps (Fig. 6) and there is a post-traumatic deformity of the left leg.

FIG. 6.—Chronically infected fingers with destruction of terminal phalanges.

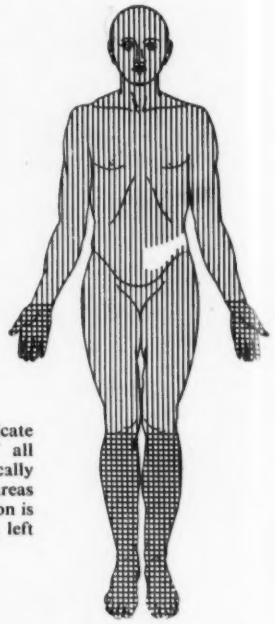

FIG. 7.—Crosshatched areas indicate total loss of appreciation of all modalities of sensation. Vertically lined areas indicate additional areas of insensitivity to pain. Sensation is normally perceived only in the left lower abdominal quadrant.

On examination of the cranial nerves the following abnormalities have been found: there is a complete inability to detect or differentiate the odours of lavender, cloves, and tincture of asafoetida. He raises no objection when his food is heavily adulterated with salt, sugar, or quinine, which observation suggests a total absence of taste. Visual acuity of the right eye is 6/12 and of the left 6/9; the reduction on the right side is due to a post-traumatic corneal opacity. There is complete loss to pain over all three divisions of the fifth nerve bilaterally with absent corneal reflexes: touch is appreciated over all three divisions, but the threshold is raised. He neither lacrimates at the smell of ammonia nor sneezes on the inhalation of snuff. Motor function of the fifth nerve is normal. There is no facial weakness. The gag reflex is absent, yet pricking of the posterior pharynx is reported by him as painful and stimulation of the trachea with a rubber catheter causes coughing. There is neither weakness nor wasting of the muscles of the trunk and upper limbs. Owing to contractures resulting from the fractured patella, extension at the left knee and hip joints is defective. Tendon reflexes are entirely lacking. The plantar responses are flexor. Only the lower abdominal skin reflexes are obtainable. Pinching and heavy pinprick are perceived as painful only over dermatomes T-10 and T-11 on the left side, and are associated with alteration in the respiratory rhythm, tachycardia, pupillary dilatation,

rotesting, and evasive movement (Fig. 7). Light touch is ppreciated at normal thresholds over the thorax, here anteriorly it causes a sensation of tickle. The hreshold for touch rises progressively as testing proeeds peripherally on the extremities until eventually he stimulus is not appreciated on the hands or feet. Vhen he perceives touch he is able to localize the area timulated with a fair degree of accuracy. Recognition f temperature differences is absent throughout except ver the dermatomes T-10 and T-11 on the left where the hreshold is within normal limits. Recognition of movement is absent at the joints of the fingers and toes, somewhat less impaired at the ankle and wrist and apparently ormal at the elbow and knee joints. Vibration is ppreciated throughout except on the fingers and toes, ut the threshold is greatly raised in the hands and feet. Ability to recognize objects and two-point discrimination re absent in the hands. An electrical stimulus of 100 volts applied to the extremities or face occasions no comment from the patient, even though it causes violent muscular contractions. The threshold for recognition of such stimuli is about 70 volts in the arms and legs, and 35 volts over the thorax and abdomen with the exception of the tenth and eleventh thoracic dermatomes on the left, where a normal threshold of 15 volts is to be found. Even 100 volts are not perceived in the hands and feet. There is also an absence of the appropriate response to stimulation of a painful character such as severe compression of the tendo Achillis and testes, or following immersion of the hands or feet in water at 4° C. There is apparently no pain in the muscle after 120 contractions of the fist in two minutes with a blood pressure cuff on the arm inflated to 220 mm. Hg. Dr. Hallpike reports that there is marked high tone deafness of the right ear only, and that vestibular function is normal. Examination for the state of the cutaneous axone reflexes has been carried out by the intracutaneous injection of histamine phosphate. A normal histamine flare response has only been elicited over T-10 and T-11 dermatomes on the left, but nowhere else. Itching powder applied generously causes no reaction except over the left tenth and eleventh thoracic dermatomes where itching and erythema occur.

The afferent mechanisms of deeper structures have also been investigated. Carotid body massage and carotid artery occlusion applied manually have caused no more change in pulse rate than during resting respiration. Four milligrams of sodium cyanide given intravenously with continuous spirographic control caused no change in rate or depth of respiration; hyperpnoea, which is the normal response, has not been observed (Heymans, 1955). When cystometrography is carried out the patient is aware of, but undistressed by, the catheter being passed. Strong contractions of the bladder associated with a desire to void occur with a volume of 25 ml. and again with 50 ml.: thereafter the bladder may be rapidly distended up to the level of the umbilicus (300 ml.) without further contractions or discomfort and with only a moderate gradual rise in pressure. Again, colic-producing drugs cause no discomfort. Sweating is normal throughout, as is the psychogalvanic skin response to startle produced by striking a gong or flashing a bright light. On the other hand, cutaneous

FIG. 8.—Interdigital nerve of the right foot. Note the very great diminution in number of myelinated fibres. (Osmic acid stain × 300.)

stimuli usually accepted as painful result in no autonomic response. Frequent examination by palpation of the peripheral nerves has failed to reveal any thickening.

Radiological studies show destruction of the terminal phalanges of the fingers and roughening with irregularity of the joint surfaces of the left knee. Films of the skull and spine show no bony abnormality. Air encephalography carried out at the age of 3 years showed a normal-sized ventricular system. No enlargement of the cisterns or sulci was seen. Electroencephalographic studies, kindly undertaken by Dr. Cobb, have repeatedly shown background activity considered normal for his age but with scattered spiking and sharp wave activity and without evidence of focal abnormality. The alpha rhythm blocks normally with eye opening. Dr. Dawson has been unable to record through the scalp from over the sensorimotor area the presence of evoked potentials on repeated electrical stimulation of the ulnar nerve which has been of sufficient strength to cause marked contractions of the muscles supplied by that nerve (Dawson, 1956). The cerebrospinal fluid on several occasions has been normal, as have been studies of the urine and blood. Serological tests for syphilis have been negative.

Histological studies, including osmic acid stains, of interdigital nerve and skin from the dorsum of the left foot showed the nerve bundles to be filled with shrunken endoneural tubes and only one or two myelinated fibres were seen in the skin (Fig. 8).

To sum up, this is an 11-year-old boy of fair intelligence who is unable to feel any form of stimulus applied to the distal parts of the extremities and who does not respond in the normal manner to extremely painful stimuli applied anywhere except over the left side of the abdomen where the threshold appears to be normal. The absence of reaction to pain is noted with a great variety of painful stimuli and has led to severe skin and bone trauma. The sensory defect is not accompanied by any obvious deficit in power of the muscles or by any muscular wasting. Again he sweats on the extremities and has a normal galvanic skin response to sudden noise or flashes of light. His main disability is thus one affecting the afferent mechanisms from the skin of the face, trunk, and limbs. Besides the defect of skin sensation there is a marked diminution in the response to stimulation of the carotid body, bladder, and gut. As the flare response over the limbs and trunk, apart from the small area in which painful sensations are perceived, is lacking it has been assumed that the peripheral sensory neurones have degenerated. This assumption has been confirmed by histological studies of a sensory peripheral nerve and skin. To permit somatic motor and autonomic functions the appropriate motor and autonomic nerves must be intact. A lesion which causes sensory neurone degeneration yet spares motor and autonomic fibres is most reasonably placed in the posterior root ganglion. This case differs from the hereditary form of sensory neuropathy in that it shows no family history of the disease, the onset is from birth, the involvement, including several cranial nerves, is much more widespread and it is not progressive. We believe that the presence or absence of progression is of sufficient importance to justify grouping our second and third cases respectively as "progressive" and "non-progressive" sensory neuropathy.

Discussion

We have listed in Table I the distinguishing features of the several conditions under discussion which may be found in the "sensory syndrome", a condition showing defective reaction to painful stimuli. The first, congenital indifference to pain, is relatively rare but probably occurs more commonly than is generally appreciated. If such a diagnosis is to be meaningful certain diagnostic criteria have to be met in addition to that of defective reaction to painful stimuli. The most important is the absence of a demonstrable lesion involving the sensory pathways. Secondly, various forms of stimulation have to be appreciated at normal thresholds, while tendon reflexes should be normal. The only abnormality is a defective reaction to strong noxious stimuli, namely an indifference to the usual painful element. Thus the integrity of sensory paths distinguishes congenital indifference to pain from the sensory radicular neuropathies. A third important criterion is that the patient must not be mentally deficient or suffer from any obvious cerebral pathology. This is a necessary qualification in order to exclude from the group those patients with gross mental defect: it is known that mental defectives may show considerable indifference to pain (Couston, 1954). Again, since Schilder and Stengel first coined the term "pain asymbolia" (1928 a and b, 1931), a number of reports have appeared dealing with indifference to pain as a symptom of cerebral pathology (Hemphill and Stengel, 1940; Pötzl and Stengel, 1936; Rubins and Friedman, 1948); a degree of indifference may occur after prefrontal lobotomy (Freeman and Watts, 1946). Riley (1952) has described a familial condition in which have been present defective lachrymation, emotional instability, areflexia, hypertension, vomiting, and indifference to pain. As most of his patients have been mentally defective and suffered from epilepsy, it is possible

TABLE I

SIMILARITIES AND DISSIMILARITIES OF CONGENITAL INDIFFERENCE TO PAIN, CHRONIC PROGRESSIVE SENSORY NEUROPATHY, AND NON-PROGRESSIVE SENSORY NEUROPATHY COMPARED

		Congenital	Progressive Sensory Neuropathy of Children	Non-progressive Sensory Neuropathy of Children
Characteristics of the sensory syndrome	Defective appreciation of pain	+	+	+
	Motor involvement	0	0	0
	Repeated self injury	+	+	+
	Disorganized joints	+	+	+
	Sensory deficit (other than pain)	0	+	+
	Distribution of sensory deficits (all types)	Universal	Greatest distally, sparing thorax and cranial nerves except 8th nerve	Greatest distally, may involve all sensory nerves
Deep tendon reflexes		Normal	Absent in involved areas	Absent in involved areas
Axone reflex		Normal	Absent in involved areas	Absent in involved areas
Sensory nerve biopsy		Normal	Demyelination	Demyelination
Hereditary transmission		0	?	0
Location of "lesion"		Central to dorsal root ganglion	In or distal to dorsal root ganglion	In or distal to dorsal root ganglion
Course		May improve with age	Slow progression	No change

hat the indifference to pain has been but a manifestation of mental deficiency. Hysteria has also been nentioned as a diagnostic possibility and properly lismissed by most authors since the condition under liscussion is present from early infancy, an age at vhich hysteria is accepted as not occurring. We feel hat it is important to apply the label of 'congenital indifference to pain" only to those patients with normal intelligence and with no demonstrable neurological abnormality. Using such criteria the cases published by the following authors seem to fit this group: Dearborn (1932), Kunkle and Chapman (1943), Boyd and Nie (1949), McMurray (1950) (also described by Petrie, 1953, and Feindel, 1953), Nissler and Parnitzke 1951), Kipnis, Cohen, Kubzansky, and Kunkle (1954) (also reported by Cohen, Kipnis, Kunkle, and Kubzansky, 1955), Julião and Brotto (1955), Jéquier and Deller (1956), Schachter (1956) and Durand and Belotti (1957). Ford and Wilkins (1938) described three cases. The first and third are typical but the second case is questionable since the patient was mentally deficient, had grand mal epilepsy and mentally defective parents. Of the four cases reported by Jewsbury (1951) three are acceptable but the fourth is unsubstantiated. Lamy, Garcin, Jammet, Aussannaire, Lambert, Thiriez, and Grasset (1956) reported two cases, the second of which (with muscle hypotonia and areflexia) should be excluded. Fanconi and Ferrazzini (1957) described three cases, the second of which was not examined and should therefore not be included in this group. We believe that the patients reported by Arbuse, Cantor, and Barenberg, (1949) having an I.Q. of 50, of Keizer (1951) being a Mongol idiot, and of Madonick (1954) with an I.Q. of 61, should not be included in this group since marked mental deficiency was such a prominent feature. Similarly the patient described by Roe and Leys (1950), who was examined by one of us (E.A.C.) through the kind permission of the authors, was found to have an I.Q. of 50 and accordingly cannot be placed in this group. The case described by Moffie (1951, 1952) is complicated by organic brain damage and psychosis, making it difficult to evaluate; again, the case described by Farquhar and Sutton (1951) had tremor of the head and hands, slurred speech, unsteady gait, and a history of meningitis at the age of 1 year. (We wish to thank the authors for permission to examine this patient.) The patient described by Ortiz de Zarate (1955) clearly has histologically proven sensory neurone degeneration, absent ankle reflexes, and a psychosis, which removes the case from the group distinguished by congenital indifference to pain. The cases briefly described by Critchley (1934, 1935), von Hagen and Grain in discussing Boyd and Nie's paper (1949), and Ziegler and Pacella in discussing Madonick's paper (1954) may belong to this group, but without more clinical details a definitive diagnosis cannot be made with any confidence.

As to the nature or region of the dysfunction responsible for the symptoms and signs as found in congenital indifference to pain, we have no helpful observations to contribute. The literature also is remarkably lacking in observational studies.

Denny-Brown directed attention to the occurrence of degeneration of posterior root ganglia secondary to carcinoma of the bronchus (1948) and later as a nosologically distinct hereditary disease (1951). His work helped to terminate a controversy lasting for years concerning the underlying pathology. In the past they had been diagnosed as cases of status dysraphicus, Morvans' disease, and syringomyelia (Schultze, 1917; Guillain and Thévenard, 1929; Thévenard and Coste, 1935; Thévenard, 1942; Parks and Staples, 1945). Several exhaustive clinical and pathological studies of hereditary sensory radicular neuropathy have appeared in recent years (Thévenard, 1953; van Bogaert, 1953; Girard, Mazare, and Devic 1953; Girard, Devic, and Garin, 1953; Heller and Robb, 1955; Roger and Pujol, 1955), and as the number of reports has grown it has become apparent that many of the cases of non-carcinomatous sensory neuropathy do not fit into the clinical picture defined by Denny-Brown (1951). The patient described by Ionesco, Ionasesco, and Mester (1958) is a case in point; a young woman, normal until the age of 17 years, shortly after a severe "T.A.B. post-vaccinal reaction" necessitating admission to hospital, developed a generalized hypaesthesia with lightning pains in the legs. By the age of 20 she presented the typical "sensory syndrome" picture with perforating ulcers of the feet, loss of several toes, and a left corneal ulcer associated with disturbance of sensation over the first division of the left fifth cranial nerve. The sensory deficit has not progressed. She showed no motor involvement. No family history of neurological disease could be elicited. The findings in this patient closely resemble those of our case (R.M.), except that this came on in early adult life. She may well represent an instance of non-progressive sensory neuropathy.

The patient described separately by Munro (1956) and by Walker (1955-56) has been examined recently by one of us through the courtesy of Dr. P. Sandifer. This is a boy, now aged 13 years, whose parents are first cousins. He has been noted to be indifferent to painful stimuli since infancy and presents as a typical case of the "sensory syndrome" with rather more involvement of the lower than the upper extremities. Perforating ulcers of the left foot have

led to a mid-tarsal amputation. That he is suffering from a neuropathy has been confirmed by biopsy of an interdigital sensory nerve. There is no motor involvement. This case is interesting for several reasons. The family history is negative for neurological disease. The patient has a moderate low tone deafness, and although he can hear a conversational tone quite clearly his verbal comprehension is extremely poor. His I.Q. on performance testing is well above average (I.Q. 110) but on verbal testing is severely defective (I.Q. 50). Careful comparison of past examinations with ours revealed no evidence of progression of the sensory deficit. We wish to suggest that this child probably has a non-progressive sensory neuropathy similar to that of our case (R.M.).

The cases reported by Parks and Staples (1945), Ortiz de Zarate (1955), and Head (1903), to name but a few, probably also represent the non-progressive rather than the progressive form of sensory neuropathy.

Summary

The "sensory syndrome", a non-specific clinical picture by which several aetiologically unrelated conditions may manifest themselves in children, is described. Its outstanding features are insensitivity or indifference to pain with failure to avoid noxious stimuli and repeated self injury. There may be a marked susceptibility to infection with perforating ulcers of the feet, osteomyelitis, and loss of terminal phalanges of fingers and toes. Disorganized joints are common.

Cases are presented to illustrate three unrelated instances of the "sensory syndrome" in children. (1) Congenital indifference to pain, a condition in which, as far as can be determined, the patient's sensory apparatus is intact, but he fails to react normally to painful stimuli. (2) Progressive sensory radicular neuropathy, a sensory neurone degeneration in the distal parts of the extremities which involves the feet more than the hands and is progressive. It is clinically indistinguishable from hereditary sensory radicular neuropathy and may represent sporadic instances of this disease. (3) Non-progressive sensory neuropathy, a widespread sensory neurone degeneration involving cranial and thoracic nerves as well as those of the limbs. The deficit is more scattered and asymmetrical than in the progressive disease and there is no progression. The aetiology of these diseases is unknown.

References

Arbuse, D. I., Cantor, M. B., and Barenberg, P. A. (1949). *J. Pediat.* **35**, 221.
Bogaert, van L. (1953). *Acta neurol. belg.*, **53**, 37.
Boyd, D. A., and Nie L. W. (1949). *Arch. Neurol. Psychiat. (Chicago)* **61**, 402.
Clark, D., Hough, H., and Wolff, H. G. (1936). *Arch. Neurol. Psychiat. (Chicago)*, **35**, 1054.
Cohen, L. D., Kipnis, D., Kunkle, E. C., and Kubzansky, P. E. (1955) *J. abnorm. soc. Psychol.*, **51**, 333.
Couston, T. A. (1954). *Brit. med. J.*, **1**, 1128.
Critchley, M. (1934). *Ibid.*, **2**, 891.
—— (1935). *Bristol med.-chir. J.*, **52**, 191.
—— (1956). *Ann. intern. Med.*, **45**, 737.
Dawson, G. D. (1956). *J. Physiol. (Lond.)*, **131**, 436.
Dearborn, G. (1932). *J. nerv. ment. Dis.*, **75**, 612.
Denny-Brown, D. (1948). *J. Neurol. Neurosurg. Psychiat.*, **11**, 73.
—— (1951). *Ibid.*, **14**, 237.
Durand, P., and Belotti, B. M. (1957). *Helv. paediat. Acta*, **12**, 116.
Fanconi, G., and Ferrazzini, F. (1957). *Ibid.*, **12**, 79.
Farquhar, H. G., and Sutton, T. (1951). *Lancet*, **1**, 827.
Feindel, W. (1953). *J. Bone Jt Surg.*, **35B**, 402.
Ford, F. R. and Wilkins, L. (1938). *Bull. Johns Hopk. Hosp.*, **62**, 448.
Freeman, W., and Watts, J. W. (1946). *Lancet*, **1**, 953.
Girard, P. F., Devic, M., and Garin, A. (1953). *Rev. neurol.*, **88**, 198.
——, Mazare, Y., and Devic, M. (1953). *Acta neurol. belg.*, **53**, 82.
Guillain, G., and Thévenard, A. (1929). *Ann. Med.*, **25**, 267.
Head, H. (1903). *Lond. Hosp. Gaz.*, Clinical Supplement. **10**, 5.
Heller, I. H., and Robb, P. (1955). *Neurology (Minneap.)*, **5**, 15.
Hemphill, R. E., and Stengel, E. (1940). *J. Neurol. Psychiat.*, **3**, 251.
Heymans, C. (1955). *Pharmacol. Rev.*, **7**, 119.
Hicks, E. P. (1922). *Lancet*, **1**, 319.
Ionesco, I., Ionasesco, V., and Mester, Z. (1958). *Acta neurol. belg.*, **58**, 260.
Jéquier, M., and Deller, M. (1956). *Confin. neurol. (Basel)*, **16**, 207.
Jewsbury, E. C. O. (1951). *Brain*, **74**, 336.
Julião, O. F., and Brotto, W. (1955). *Arch. Neuro-psiquiat. (S. Paulo)*, **13**, 338.
Keizer, D. P. R. (1951). *Lancet*, **1**, 1020.
Kipnis, D. M., Cohen, L. D., Kubzansky, P. E., and Kunkle, E. C. (1954). *Trans. Amer. neurol. Ass.*, **79**, 105.
Kunkle, E. C., and Chapman, W. P. (1943). *Ass. Res. nerv. Dis. Proc.*, **23**, 100.
Lamy, M., Garcin, R., Jammet, M. L., Aussannaire, M., Lambert, A., Thiriez, H., and Grasset, A. (1956). *Sem. Hôp. Paris*, **32**, 2823.
McMurray, G. A. (1950). *Arch. Neurol. Psychiat. (Chicago)*, **64**, 650.
Madonick, M. J. (1954). *Neurology (Minneap.)*, **4**, 554.
Moffie, D. (1951). *Confin. neurol. (Basel)*, **11**, 219.
—— (1952). *Ned. T. Geneesk.*, **96**, 1177.
Munro, Margaret (1956). *Brit. med. J.*, **1**, 541.
Murray, R. O. (1957). *Brit. J. Radiol.*, **30**, 2.
Nafe, J. P., and Wagoner, K. S. (1938). *Amer. J. Psychol.*, **51**, 118.
Nissler, K., and Parnitzke, K. H. (1951). *Dtsch. med. Wschr.*, **76**, 861.
Ortiz de Zarate, J. C. (1955). *Encéphale*, **44**, 414.
Parks, H., and Staples, O. S. (1945). *Arch. intern. Med.*, **75**, 75.
Petrie, J. G. (1953). *J. Bone Jt Surg.*, **35B**, 399.
Pötzl, O., and Stengel, E. (1936). *Jb. Psychiat. Neurol.*, **53**, 174.
Riley, C. M. (1952). *J. Amer. med. Ass.*, **149**, 1532.
Roe, W., and Leys, D. G. (1950). *Proc. roy. soc. méd.*, **43**, 250.
Roger, J., and Pujol, R. (1955). *Marseille-méd.*, **92**, 159.
Rubins, J. L., and Friedman, E. D. (1948). *Arch. Neurol. Psychiat. (Chicago)*, **60**, 554.
Schachter, M. (1956). *Praxis*, **45**, 681.
Schilder, P., and Stengel, E. (1928a). *Z. ges. Neurol. Psychiat.*, **113**, 143.
——, —— (1928b). *Klin. Wschr.*, **7**, 535.
——, —— (1931). *Arch. Neurol. Psychiat. (Chicago)*, **25**, 598.
Schultze, F. (1917). *Dtsch. med. Wschr.*, **43**, 545.
Thévenard, A. (1942). *Rev. neurol.*, **74**, 193.
—— (1953). *Acta. neurol. belg.*, **53**, 1.
——, and Coste, M. (1935). *Rev. neurol.*, **63**, 195.
Walker, C. H. M. (1955-56). *Gt Ormond Str. J.*, No. 10, p. 72.
Walter, W. G., and Ritchie, A. E. (1945). *Electronic Engng*, **17**, 585.
Wolf, S., and Hardy, J. D. (1941). *J. clin. Invest.*, **20**, 521.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 277

THE NON-SPECIFICITY OF THE INTRATHECAL REACTION TO TUBERCULIN IN MULTIPLE SCLEROSIS

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The intrathecal injection of the purified protein derivative of tuberculin (P.P.D.) was used by Smith, Vollum, Taylor, and Taylor (1956) in the treatment of tuberculous meningitis. They had been led to use this method by the observation that the cellular and protein content of the cerebrospinal fluid of patients with tuberculous meningitis showed marked fluctuations which they believed to be due to the liberation of tubercular protein into the sensitized meninges. The presence of these fluctuations was associated with clinical improvement; hence they wondered whether this effect could be reproduced by the intrathecal injection of tuberculin. Considerable success was achieved with this method of treatment.

The injection of P.P.D. in patients with tuberculous meningitis produced a characteristic disturbance of the cellular and protein content of the cerebrospinal fluid. This consisted of a brisk outpouring of predominantly polymorphonuclear cells within the first 24 hours accompanied by a similar rise in protein. This was followed by a wave of mononuclear cells maximal between the third and seventh days after injection, there again being an accompanying rise in protein. A similar reaction, though often of less degree, was observed in a group of Mantoux-positive psychotic patients (Swithinbank, Smith, and Vollum, 1953). A further feature was that there appeared to be a correlation between the sensitivity of the meninges and that of the skin to tuberculin. In patients who were Mantoux-negative only a minimal disturbance was produced in the cerebrospinal fluid by the intrathecal injection of P.P.D., but the typical pattern of response could be obtained after successful vaccination of the patient with B.C.G. or vole bacillus.

More recently it has been found that in patients with multiple sclerosis the pattern of response is different from that seen in psychotics (Smith, Espir, Whitty, and Russell, 1957). These authors observed that the initial 24-hour spike of cells was absent, but the subsequent wave of mononuclear cells was well developed; in addition there was a biphasic rise in protein. The authors comment that there was a tendency for the protein rise to outstrip that of the cells. They observed no correlation between the sensitivity of the skin and that of the meninges in these patients. A similar type of reaction could be obtained in highly sensitive psychotic patients in whom the intrathecal injection of P.P.D. was covered by a small dose of cortisone. They interpreted these findings as indicating that the normal immunological processes are disordered in multiple sclerosis. They further suggested that the intrathecal injection of P.P.D. might have beneficial therapeutic effects in this disease.

Since no other chronic neurological diseases had been treated in this way, and there was therefore no reason to believe that the changes described were specific to multiple sclerosis, it seemed possible that the therapeutic benefit might be obtained in other conditions. In addition the belief that the type of reaction obtained in multiple sclerosis reflected a specific immunological abnormality made it essential to establish whether similar changes occurred in other diseases. We have therefore offered this treatment to patients with other incurable neurological diseases.

Material and Methods

Seventeen patients with multiple sclerosis, nine with motor neurone disease, three with Huntington's chorea without dementia, and three with Parkinsonism, all of whom were Mantoux-positive, have been treated. No patient was in the terminal stages of the disease. Their ages are shown in Table I.

In each case the first injection of P.P.D. was given on a Monday after removal of cerebrospinal fluid for examination. The cerebrospinal fluid was re-examined on Tuesday, Wednesday, and Friday. On the following Monday, if no clinical response had occurred, this procedure was repeated using a larger dose. The dose of P.P.D. used for each patient is set out in Table I. With increasing familiarity with the clinical response larger initial doses were employed.

TABLE I

DETAILS OF CEREBROSPINAL FLUID RESPONSE IN THE PRESENT SERIES

No.	Age	Sex	Mantoux Positive at	Dose of P.P.D. (µg.)	Type of Response	24 Hours			48 Hours			Maximum 3-8 Days		
						Total Cells	Polymorphs (%)	Protein	Total Cells	Polymorphs (%)	Protein	Total Cells	Polymorphs (%)	Protein
Multiple Sclerosis														
1	27	M	5	0·0375	b	113	63	154	80	80	171	256	3	118
2	28	F	5	0·0375	a							59	0	300
				0·1875	b	236	0	900	344	0	800	260	0	700
3	26	M	5	0·0375	b	298	96	130	148	13		266	6	200
				0·1875	b	490	6	800	320	24	375	549	3	400
4	35	F	4	0·0375	a					3		69		45
				0·1875	b	509	3	360	280	12	190	422	1	184
5	41	M	4	0·0375	nil									
				0·1875	b	193	21	370	12	1	225	176	1	65
6	30	F	3	0·01875	a							94	2	132
				0·0375	b	415	25	270	658	8	91	177	4	91
7	44	M	3	0·01875	a							72	0	84
				0·0375	a							55	7	49
				0·1875	a							35	0	81
8	56	M	3	0·0375	a							258	0	198
				0·1875	b	234	2	660	320	6	650	567	0	223
9	27	F	3	0·1875	a							56	0	140
				0·375	b	190	0	450	215	0	200	129	0	300
10	47	M	3	0·375	b	370	20	85	18	6	150	81	0	80
				0·1875	b	150	31	500	13	7	350	232	4	300
11	55	M	3	0·375	a							27	15	90
				0·1875	a							195	0	440
12	28	M	3	0·1875	b	101	0	140	387	0	200	212	0	280
13	41	M	3	0·0375	a							77	1	140
				0·1875	a							550	0	4400
14	26	F		0·1875	nil									
			2	0·375	a							43	0	100
15	48	F		0·0375	b	1,380	80	170	146	60	100	35	10	120
			2	0·1875	b	196	31	350	402	29	150	375	0	250
16	42	M		0·375	a							18	6	80
			2	0·1875	b	406	42	300	268	31	220	205	1	225
17	38	M		0·375	a							90	3	80
			2	0·1875	b	191	30	325	190	18	450	152	0	250
Motor Neurone Disease														
18	55	M	4	0·1875	a							330	0	450
19	52	M	4	0·1875	a							148	0	250
20	61	M	3	0·0375	a							196	13	90
				0·1875	a							374	2	140
				0·375	b	951	25	500	790	2	275	883	2	300
21	39	M	3	0·1875	a							640	0	500
				0·375	b	660	18	500	660	18	500		0	
22	57	M	2	0·1875	nil									
				0·375	a							450	0	300
23	27	M	2	0·375	nil									
				0·1875	a							38	0	50
24	48	F	2	0·375	a							33	0	100
				0·1875	b	156	12	60	254	0	70	102	2	70
25	50	F	2	0·1875	a							57	0	70
				0·0375	b	891	22	1,000	416	12	520	719	2	450
26	69	F	2	0·1875	a							47	0	90
				0·375	b	885	17	500	535	48	200	600	0	200
Huntington's Chorea														
27	37	F	4	0·375	b	134	94	80	146	13	100	139	0	85
				0·1875	b	653	30	850	402	20	150	314	7	275
28	46	M	4	0·1875	a							382	1	200
29	45	M	3	0·1875	a							67	9	100
				0·375	b	753	15	2,000	81	22	800	842	0	450
Parkinson's Disease														
30	37	F	3	0·1875	a							40	0	180
31	59	M	2	0·1875	a							50	0	240
				0·375	b	130	5	1,000	116	1	175	114	2	280
32	43	F	2	0·1875	a							87	3	80
				0·375	b	179	2	600	226	3	240	1,031	3	300

The Clinical Response.—This was characterized by headache, neck stiffness, fever, vomiting, and in many cases drowsiness. Patients who did not develop these symptoms were completely unaffected.

Examination of the Cerebrospinal Fluid.—Cell counts were performed in the Fuchs Rosenthal chamber and preparations of the centrifuged deposit stained by Leishman's method. All the examinations were made by one of us (F.O'G). Protein was estimated in the first 15 cases by a micro-Kjeldahl method. Subsequently a nephelometric method was employed and a correction was applied (J. Arthur, personal communication).

Skin Testing.—Doses of 10, 1, 0·1, and occasionally 0·01 tuberculin units (t.u.) were given on the day on which the first intrathecal injection of P.P.D. was made (1 t.u. is contained in 0·1 ml. of 1 in 10,000 dilution of

tuberculin). Separate syringes were used for each dilution and separate needles for each patient. The injections were made in order on the anterior aspect of the forearm so that the greatest dilution was most distal. The areas of erythema and induration were measured daily and recorded as previously described (O'Grady, 1956). Patients who failed to respond were tested with 100 t.u. at the time the second dose of intrathecal P.P.D. was given.

Results

Results in Multiple Sclerosis.—The intrathecal injection of the first dose of P.P.D. produced no response in the cerebrospinal fluid of two patients and a slow rise of cells in 10 of the 17 patients. This slow rise of cells was called the "a" type response. The administration of a second dose one week after the first to one of the patients (Case 14) who had no cellular response produced an "a" type response in the cerebrospinal fluid accompanied by a clinical response; hence she was given no further P.P.D. Likewise two of the 10 patients (Cases 11 and 13) gave a second "a" type response, and one patient (Case 7) a third, accompanied by a clinical response, and they were given no more P.P.D. The second patient who had failed to respond to the first dose (Case 5) and the remaining seven of the 10 patients who had given an "a" response produced a different type of reaction to their second dose of P.P.D. This was characterized by a peak of cells maximal within 48 hours which subsequently settled to a plateau, or was followed by a further wave of cells maximal between the third and the seventh day. This latter type of response we have called the "b" type. Five of the 17 patients gave only the "b" type response. Three of these patients had two "b" type responses, the first of which was not accompanied by a clinical reaction. In the "a" type response more than 90% of the cells were mononuclear, except in one case (Case 11) where 15% of polymorphs were found. Similarly, the predominant cell in the "b" type response was again the mononuclear, and in nine of the 13 cases the percentage of polymorphs did not exceed 31. In the remaining four patients, two of whom gave two "b" type responses (Cases 3 and 15), the percentage of polymorphs in the first response was 63, 96, 80, and 42. Details of these responses are set out in Table 1.

During the "a" type response the protein showed a slow rise maximal between three and seven days. Associated with the "b" type response the protein showed a sharp peak within the first 48 hours followed by a plateau or a second less sharp increase. A typical combination of "a" and "b" type response is shown in Fig. 1. The frequency with which "a" and "b" type responses were encountered are given in Table II. The maximum, minimum, and mean cellular and protein responses during the "a" type responses are shown in Fig. 2, and in the "b" type response in Fig. 3.

TABLE II

FREQUENCY OF TYPE OF RESPONSE IN EACH NEUROLOGICAL DISEASE

	Multiple Sclerosis	Motor Neurone Disease	Parkinsonism and Huntington's Chorea	Total
"a" type only	4	4	2	10
"b" type only	6	—	1	7
"a" and "b" type	7	5	3	15
Total	17	9	6	32

Results in Other Conditions.—The results in the three other chronic neurological diseases which we have studied differed in no essential from those described above. Of the nine cases of motor neurone disease, four gave an "a" type response and five "a" plus "b" type responses. The percentage of polymorphs did not exceed 13 in the "a" type responses and 50 in the "b" type responses. In the two other conditions, Huntington's chorea and Parkinsonism, two of the six patients gave an "a" type response, one a "b" type, and three an "a" plus "b" type. The similarity between the results in the various conditions is shown in Figs. 1, 2, and 3.

Skin Sensitivity to Tuberculin.—Two patients who were suffering from Parkinsonism and proved to be Mantoux-negative are not included in the series. In one the injection of 0·1875 μg. and subsequently 0·375 μg. P.P.D. produced a minimal disturbance in cells and protein. In the other the injection of 0·1875 μg. P.P.D. produced a maximum of 150 cells at 24 hours of which 50% were polymorphs with no change in protein. In the Mantoux-positive patients there was no direct correlation between the degree of skin sensitivity to tuberculin and the magnitude of the response in the cerebrospinal fluid (Table I).

Discussion

From the analysis of the temporal pattern of the responses in number and types of cells and the amount of protein, there appear to be two types of response in the present series. The first, which we have called the "a" type response, is characterized by a slow steady rise in the levels of cells and protein. The second, "b" type response, consists of a peak of cells and protein within the first 48 hours, followed by a plateau or second wave of cells and protein maximal between the third and seventh days. The type of cell does not appear to be a criterion by which the responses can be differentiated

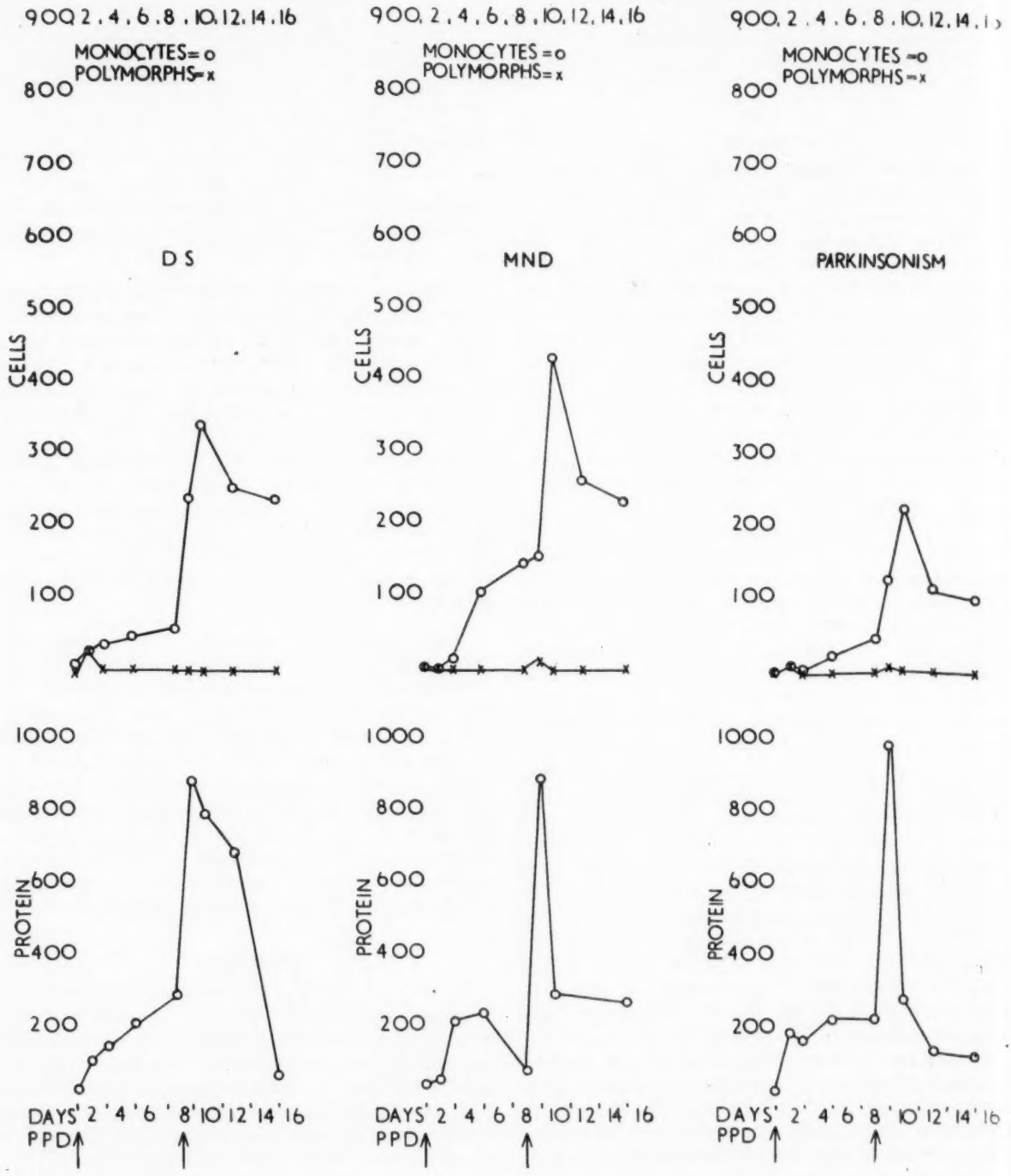

FIG. 1.—Typical examples of the "a" plus "b" type responses in multiple sclerosis, motor neurone disease, and Parkinsonism.

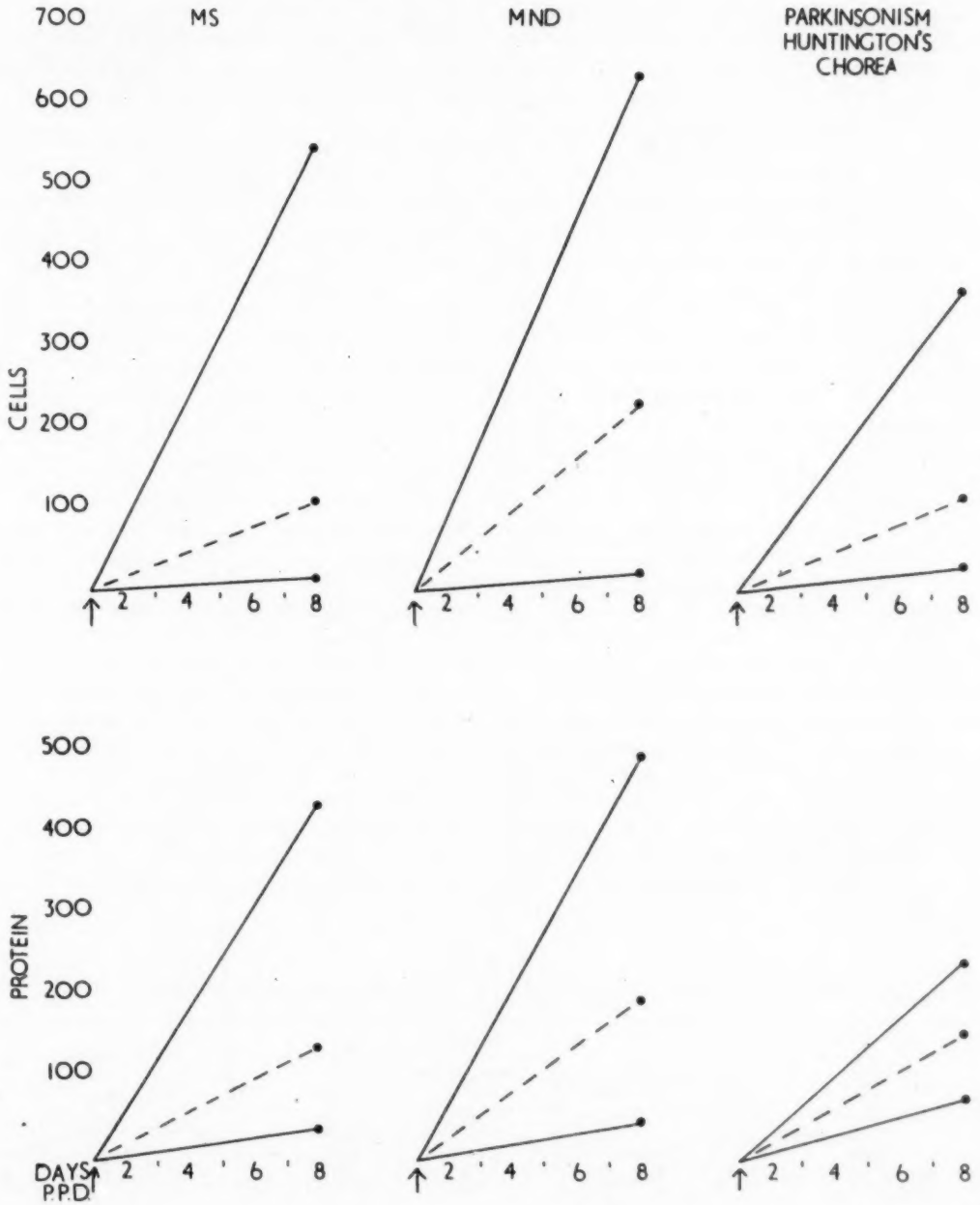

FIG. 2.—A comparison of the maximum, minimum, and mean cells and protein in the "a" type response in the 17 patients with multiple sclerosis, nine with motor neurone disease, and six with Parkinsonism or Huntington's chorea.

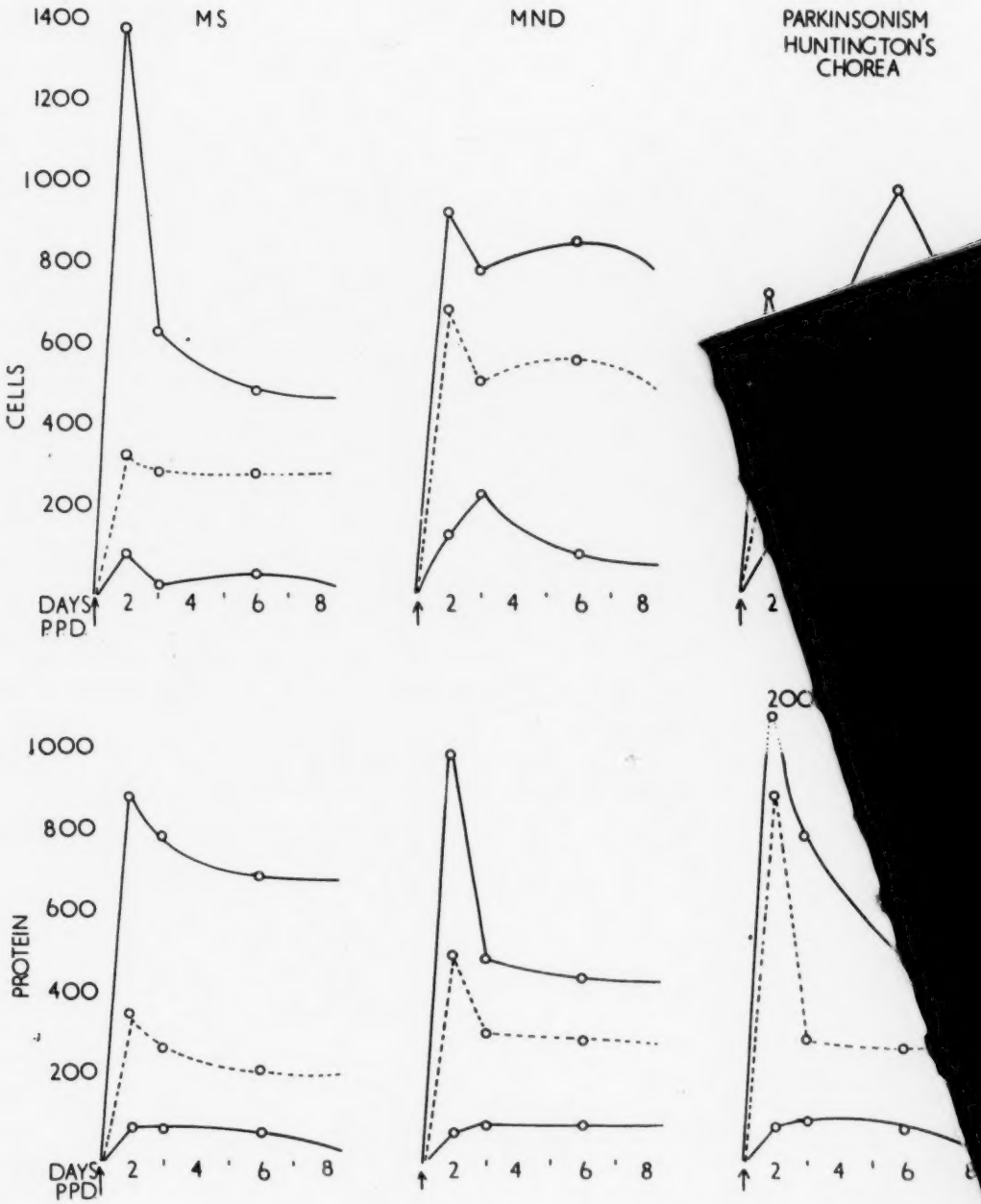

FIG. 3.—A comparison of the maximum, minimum, and mean cells and protein in the "b" type response in the 17 patients with multiple sclerosis, nine with motor neurone disease, and six with Parkinsonism or Huntington's chorea.

for the polymorphs ranged from 0 to 96% in a smooth continuum.

When the case material is examined according to the type of response there was no difference among the four chronic neurological diseases which were studied. Especially, the pattern found in multiple sclerosis differed in no essential feature from found in the other three conditions. This not support the view of Smith et response in multiple sclerosis condition.

We were previ

peak after three to eight days. psychotics were tested with the patients with m variety of d selves

considerably the reported pattern of cellular response.

In the present series the rise in protein was often more conspicuous than in the psychotic group; more so in fact than in the Oxford series (Table III). Substantially raised cerebrospinal fluid protein levels for more than 10 days are, however, shown for psychotic patients in Fig. 1 and Fig. 2 of Swithinbank *et al.* (1953).

The significant difference in the psychotics is that they have a very much higher initial cell count and percentage of polymorphonuclear cells. It is possible that this difference is the result of diminished tuberculin sensitivity in the theca of patients with chronic neurological disease possibly analogous with that seen in the skin in acute infectious illnesses, Hodgkin's, and other diseases. On the other hand, the possibility that the abnormality is in the psychotic group cannot be ignored:

The present series is too small, uncontrolled, and too recently treated to permit any conclusions to be drawn as to the therapeutic value of intrathecal P.P.D. The acute reaction may be severe, with a temporary exacerbation of existing neurological signs. Loss of sphincter control is especially common and in the patients with multiple sclerosis may persist for several weeks. The severity of the reaction in some of the patients with Parkinsonism was sufficient to discourage further exploration of this method of treatment.

The final therapeutic assessment of intrathecal P.P.D. in multiple sclerosis must await the results of a controlled clinical trial. The present findings do not in any way nullify the suggestion that this treatment may be of benefit. It is clear, however, that the lack of specificity of the response in multiple sclerosis is a disappointing finding.

Summary

The response in the cerebrospinal fluid to the intrathecal injection of tuberculin has been studied in multiple sclerosis, motor neurone disease, Parkinsonism, and Huntington's chorea without dementia.

Two types of response are described, the first being a slow rise in the levels of cells and protein, and the second an abrupt rise within 24 to 48 hours followed by a second rise or plateau at three to eight days.

Both types of response are encountered in each of the four neurological diseases described. The response to intrathecal tuberculin in multiple sclerosis is not therefore specific to this disease.

References

O'Grady, F. (1956). *Brit. J. Tuberc. Dis. Chest*, **50**, 159.
—— (1957). *Ibid.*, **51**, 74.
Smith, H. V., Espir, M. L. E., Whitty, C. W. M., and Russell, W. R. (1957). *J. Neurol. Neurosurg. Psychiat.*, **20**, 1.
——, Vollum, R. L., Taylor, L. M., and Taylor, K. B. (1956). *Tubercle (Lond.)*, **37**, 301.
Swithinbank, J., Smith, H. V., and Vollum, R. L. (1953). *J. Path. Bact.*, **65**, 565.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 285

THE SEASONAL INCIDENCE OF ONSET AND EXACERBATIONS IN MULTIPLE SCLEROSIS

BY

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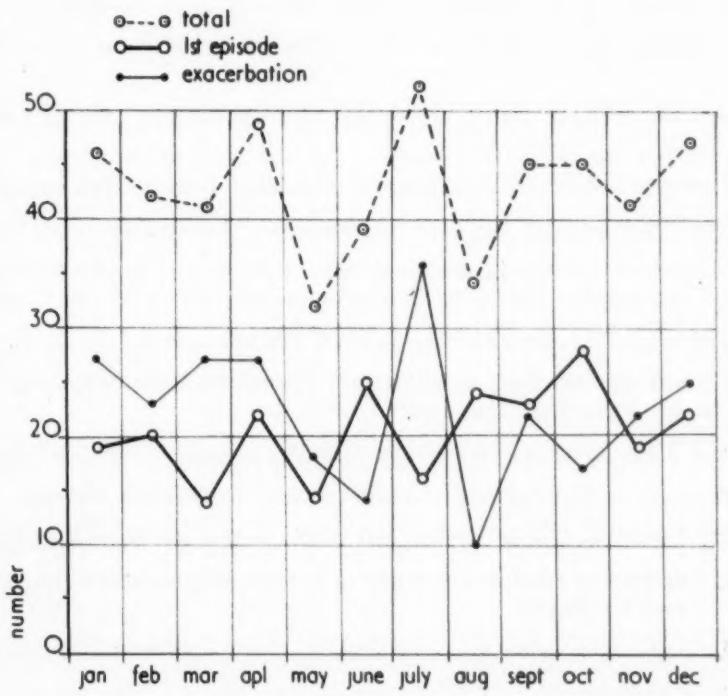
That the disease is significantly more common in the northern part of the northern hemisphere is one of the few epidemiological observations about multiple sclerosis which can be regarded as reasonably well established. The cause for this increased incidence in colder climates remains entirely obscure: an increased prevalence of upper respiratory infections or of vasospastic disorders under such conditions are amongst the possible mechanisms which have been speculatively invoked, but there is no reliable evidence in either direction.

For these reasons it was considered of interest to study the case histories of a large number of patients with multiple sclerosis personally examined in the north-east of England, to ascertain whether there was any seasonal incidence, either in the onset or in exacerbations of the established disease. There is little previous information on these lines in the literature of the subject, and Limburg, in the volume on multiple sclerosis and the demyelinating diseases, published by the Association for Research in Nervous and Mental Disorders in 1950, discusses the difficulty in assessing seasonal variations retrospectively on the basis of mortality and morbidity statistics, and suggests further observations drawn from clinical protocols, as in the present study. Hopkins and Swank (1955), in a study of patients in north-eastern Canada, found no monthly variation in incidence but noted a significant correlation with diurnal temperature range.

In many instances the onset of multiple sclerosis cannot be dated within a month, and in any case it is unlikely that the onset of symptoms coincides exactly with the initiation of the pathological lesion. It is also possible that new symptoms may be caused by one or two strategically situated lesions amongst many simultaneously initiated or re-activated, and that some pathological exacerbations may even be entirely asymptomatic. However, both the onset of symptoms and, particularly the identifiable acute exacerbations of the disease, presumably indicate at the least a critical activation of the disease process—a pathological as well as a clinical exacerbation.

Quite often, the progress of the disease is insidious throughout. Such cases were excluded from the present series but an analysis of 700 case histories yielded relevant information in 514 instances, 246 in which the onset could be clearly dated, and 268



Incidence by MONTH of Multiple Sclerosis
(analysis of 514 episodes)

identifiable acute exacerbations. The monthly distribution of these incidences, separately and in combination, is indicated in Fig. 1.

There is little difference in the incidence per month of initial episodes (x^2 with 11 degrees of freedom = 10·617—not significant). More exacerbations, however, occurred in July than in any other month, but this increase in July is balanced by a decrease in June and August. When the incidence for three-monthly periods throughout the year is compared, there is no evidence of seasonal preponderance either for total episodes (January to March, 130; April to June, 120; July to September, 131; October to December, 133) or for initial episodes or exacerbations.

The author wishes to thank the North-East Multiple Sclerosis Trust for the financial support which has made this work possible, and Dr. Henry Miller for suggesting the subject of the present investigation.

References

Limburg, C. L. (1950). *Res. Publ. Ass. nerv. ment. Dis.*, **XXVIII**, 15.

Hopkins, C. E., and Swank, R. L. (1955). *A.M.A. Arch. Neurol. Psychiat.*, **74**, 203.

THE AUGUST (1959) ISSUE

The August (1959) issue contains the following papers:—

Memories of Hugh Cairns Sir Geoffrey Jefferson.

Changes in Human Muscles after Permanent Tenotomy. S. Sunderland and J. O. Lavarack.

The Range of Conduction Velocity in Normal Motor Nerve Fibres to the Small Muscles of the Hand and Foot. P. K. Thomas, T. A. Sears, and R. W. Gilliatt.

A Clinical and Experimental Study of the Effects of Exercise on Motor Weakness in Neurological Disease. J. A. R. Lenman.

A Case of Spontaneous Dissecting Aneurysm of the Internal Carotid Artery. R. McD. Anderson and M. M. Schechter

Ruptured Posterior Fossa Aneurysms and their Surgical Treatment. Helen Dimsdale and Valentine Logue.

The Association of Cerebral Angiomas with Intracranial Aneurysms. J. S. Boyd-Wilson.

Congenital Arteriovenous Fistula with Aneurysm of the Great Cerebral Vein and Hydrocephalus Treated Surgically. James B. Gibson, Alexander R. Taylor, and Alan E. Richardson.

Traumatic Thrombosis of the Internal Carotid Artery. T. D. R. Hockaday.

Clinical and Electroencephalographic Investigations in Myoclonic Cerebellar Dyssynergia. A. Kreindler, E. Crighel, and I. Poilici.

Is Lumbar Puncture Harmful in Multiple Sclerosis? Kurt Schapira.

Slowness in Schizophrenia. Arthur Harris and Maryse Metcalfe.

The Use of an Object Sorting Test in Elucidating the Hereditary Factor in Schizophrenia. N. McConaghy.

A Clinical and Biochemical Study of a Trial of Iproniazid in the Treatment of Depression. C. M. B. Pare and M. Sandler.

A Cerebrospinal Fluid Bank. Harold C. Voris and Peter J. Talso.

Book Reviews.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s.* 6*d.*

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THE SIGNIFICANCE IN HUMAN STEREOTACTIC BRAIN SURGERY OF INDIVIDUAL VARIATION IN THE DIENCEPHALON AND GLOBUS PALLIDUS*

BY

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Access to deeply seated parts of the brain with minimal damage to structures other than the target itself was achieved in the experimental animal by Horsley and Clarke (1908). A coordinate system was employed based upon three fundamental planes, the mid-sagittal plane, a horizontal plane passing through the external auditory meati and the inferior margins of the orbits (the Frankfurt plane), and a coronal plane through the auditory meati at right angles to the latter. Thus the position of any point in the brain could be defined by three coordinates related to these three planes.

It may fairly be said that the stereotactic technique opened a new chapter in the anatomical and physiological investigation of the animal brain and a vast literature has accumulated recording the results of its application to animals of many species from rodent to primate. Nevertheless while a reasonable constancy of body weight will ensure adequate accuracy in placing the needle tip in small animals, the factor of individual variation becomes more important in larger brains. Thus for the cat, Loewenfeld and Altman (1956) have demonstrated the lack of a constant relationship between brain structures and salient landmarks in the skull. Again, in the monkey, skull shapes may vary considerably between animals of similar body weight (Olszewski, 1951).

The first application of the stereotactic principle to the human brain was made by Spiegel, Wycis, Marks, and Lee (1947) in an attempt to replace the operation of prefrontal leucotomy by interruption of thalamocortical pathways in the thalamus itself. It was recognized that coordinates of subcortical structures could never be estimated with any degree of accuracy if based upon bony landmarks alone. Further there was ". . . . great variability in the relation of the inter-aural plane to an intracerebral reference point, for example, the centre of the pineal body or of the posterior commissure" (Spiegel and Wycis, 1952).

The chapter on variability studies forms a valuable part of this atlas and while indicating the value of the technique for targets as large as the dorsomedial nucleus of the thalamus or the globus pallidus, it also provided an incentive to a search for a method that might assure greater accuracy and thereby justify operations upon the smaller diencephalic nuclei.

An important step forward consisted in the selection of a horizontal plane independent of any bony landmark and passing through midline diencephalic structures identifiable in a lateral radiograph in which the third ventricle was filled with air or a radio-opaque material. Several such horizontal planes have been used, the majority passing through the posterior commissure posteriorly, and through either the lower margin of the interventricular foramen (Hassler and Riechert, 1954) or the upper border of the anterior commissure (Talairach, de Ajuriaguerra, and David, 1952) anteriorly. The distance between these anterior and posterior points is measured in the patient's encephalogram (with correction for *x*-ray magnification) and in the "atlas" brain. The ratio between them has been used (*e.g.*, Hassler and Riechert, 1954) as a factor by which the antero-posterior coordinate of a particular nucleus in the "atlas" brain can be corrected for that of the patient. The important assumption is therefore made that these two points, but particularly the posterior commissure, maintain a constant spatial relationship to thalamic and other diencephalic structures.

The primary purpose of the present investigation was to test this assumption in a large series of human brains (Part I). From the outset it became apparent that the thalamic nuclear pattern at posterior commissure level varied considerably from case to case. An attempt was therefore made to define a more reliable landmark from which to measure the antero-posterior coordinates of thalamic nuclei (Part II).

*A preliminary communication has already been presented (Brierley and Beck, 1957).

The data emerging from both studies cannot be regarded as any form of stereotactic atlas of the diencephalon; they indicate solely individual variation and relationships and not the dimensions of individual nuclei.

Additional information has also been obtained concerning the variation in the position of the globus pallidus.

MATERIAL AND METHODS

In all, 53 hemispheres from 47 formalin-fixed and suspended brains collected from general hospitals were used in the investigation. Any brain showing the least degree of distortion (particularly of the brain-stem) was rejected. However, a number showing slight to moderate cortical atrophy or a slight to moderate degree of hydrocephalus (features likely to be present in a proportion of patients selected for stereotactic operations) were included. The weight range was 1,170 to 1,615 g.

Each brain was divided in the mid-sagittal plane. A "O" horizontal plane connecting the lower border of the interventricular foramen and the nearest point on the posterior commissure was marked with a fine needle on the medial aspect of the thalamus. This line was extended forwards across the septum pellucidum or rostrum of the corpus callosum and backwards across the midbrain tectum.

In each hemisphere the distance, V (Fig. 1a), between posterior commissure and interventricular foramen was measured and also the "total thalamic length", T, from the interventricular foramen to the point where the "O" horizontal plane intersects the posterior surface of the pulvinar.

In each of the 40 hemispheres used in the first part of this study a coronal cut was made at right angles to the horizontal plane at the level of the anterior edge of the posterior commissure. An Edinger macrotome was used to ensure that this first cut passed precisely at right angles to the mid-sagittal plane. Further parallel cuts were then placed at 3 to 5 mm. intervals, the slice thickness being adjusted so that one cut passed through the mid-thalamic point, *i.e.*, half way between the posterior commissure and the interventricular foramen, and one through the lower border of the interventricular foramen (Fig. 1a).

Histological examination was carried out on the slice adjacent to the mid-thalamic and posterior commissure planes. The "O" horizontal plane was marked on the coronal face of each by two small punch holes aligned at right angles to the sagittal plane at the level of the "O" plane itself. From each slice a block was cut to include thalamus, sub-thalamus, and a variable portion of the pallidum. Frozen sections were cut at 50 μ and stained for nerve cells (Nissl's method) and for myelin sheaths (Woelke's modification of Weigert Pal). In view of the rapid change in thalamic nuclear configuration, especially at the posterior commissure, care was taken to stain the first two sections from each block.

Projection diagrams were drawn from the sections and the "O" horizontal plane was indicated by a line passing through the two small punch holes referred to above.

In the remaining 13 hemispheres (Part II) the "O" horizontal plane was marked as before. The "total thalamic length" was then measured and coronal cuts were placed at 0, 25, 50, 75, and 100% of this value measured forwards from the pulvinar thus producing four slices of equal thickness. Projection diagrams were drawn to illustrate all but the zero percentage level; these included basal ganglia as well as thalamic structures. Myelin-stained sections of the thalamus were prepared for the 25 and 50% levels only and supplemented by Nissl-stained sections to define nuclear configuration where necessary. At the 75 and 100% levels, all structures were macroscopically visible so that the diagrams could be prepared from the slices themselves.

For the globus pallidus, the position of its lateral and inferior borders with respect to the midline and horizontal zero planes was determined at the 100, 75, and 50% levels, the medial tip at the 75 and 50% planes only. It was thus possible to compare the thalamic nuclear pattern and the position of the globus pallidus, at each percentage level in all 13 hemispheres.

RESULTS IN PART I

Relations of the Posterior Commissure (40 Hemispheres)

Antero-posterior.—The distance between the interventricular foramen and the posterior commissure (ventricular length, V) varied from 20·0 to 26·0 mm. (average 23·4 mm.). There was virtually no correlation between V and brain weight.

The total thalamic length (T) was found to vary between 31·0 and 38·0 mm. (average 34·5 mm.). There was some broad correlation between total thalamic length and brain weight, so that for any particular weight, the length T might vary up to $\pm$ 2·5 mm.

The inclination of the horizontal plane as seen on the medial surface of the hemisphere was found to be very variable. When prolonged anteriorly this line could pass anywhere between two points 1·5 mm. below and 7·0 mm. above the posterior end of the lamina rostralis of the corpus callosum.

The distance from the posterior commissure to the tip of the pulvinar (P) equals 26 to 41% of the total thalamic length and this value (referred to in the following as the "percentage value") had no relation to brain weight or to the total thalamic length itself. The difference between these two extreme percentage values was 15·4%. This implies that in a brain of average total thalamic length (34·5 mm.), the posterior commissure would lie anywhere within an antero-posterior distance of 5·3 mm.

Between the extreme positions of the posterior commissure the 40 brains could be grouped according to their percentage values as follows:—

(1) 25 to 29% in 12 specimens
(2) 30 to 34% in 15 specimens
(3) 35 to 39% in 10 specimens (+ three at 40, 40, and 41%)

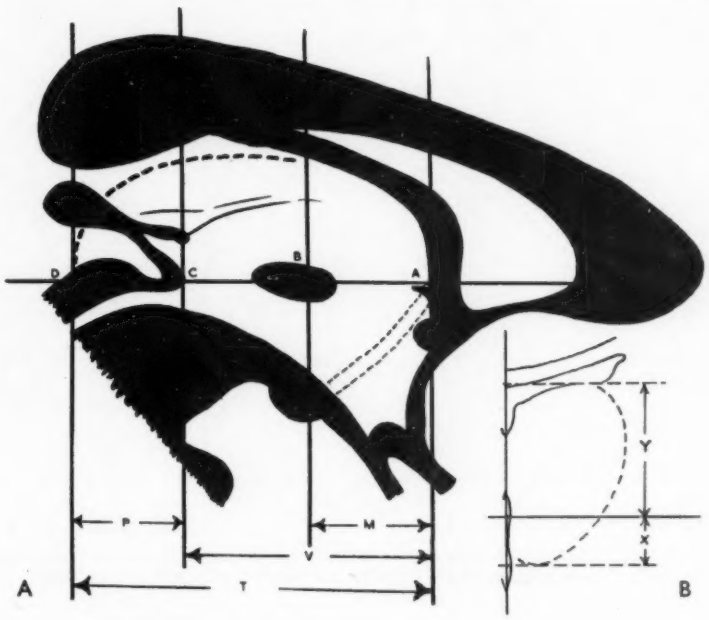

FIG. 1.—Diagram of the mid-sagittal plane indicating the horizontal plane (AC) through the lower border of the interventricular foramen and anterior curvature of the posterior commissure; extended posteriorly to intersect the pulvinar at (D) and anteriorly across the septum.

T = total thalamic length (AD)
V = ventricular length (AC)
M = half ventricular length (AB, BC)
P = length of pulvinar behind posterior commissure (CD).

B. Diagram of coronal section at mid-thalamic level to illustrate the vertical extent (X) below, and (Y) above the zero horizontal line.

25 to 29% Level.—Within this group, the more posterior nuclear pattern comprised the pulvinar and the two geniculate bodies (Fig. 2b). The more anterior pattern included, in addition, the extreme posterior tips of the centromedian nucleus and of the nucleus ventralis posterior. The geniculate bodies might be absent or only one, the lateral, might be present.

There was one exception in this group with a percentage value of 29 in which the centromedian nucleus was fully developed and the dorsomedial nucleus was also present. It thus approximated to the features of the next group.

30 to 34% Level.—Here the nuclear pattern was more uniform (Fig. 6b) and comprised the junction of the pulvinar with the dorsomedial nucleus, the nucleus lateralis posterior, and the full development of the centromedian, ventralis posteromedialis, and ventralis posterolateralis nuclei. The extreme anterior tip of the lateral geniculate body was present in five specimens.

35 to 41% Level.—The nuclear configuration differed from that in the previous group in that the dorsomedial nucleus was fully developed. The nucleus lateralis dorsalis was present in seven specimens. In all but two, the lateral geniculate body was no longer seen (Fig. 2a).

Left-right Differences.—Nine whole brains were available in which to compare left and right sides. In all nine the left and right ventricular lengths did not differ by more than 1 mm. In each of six brains in which the total thalamic lengths and thus the percentage values of the posterior commissure were very similar, there was no appreciable difference between the nuclear patterns at the level of the latter.

In three brains (Fig. 3) with identical ventricular lengths there were left-right differences in total thalamic length (up to 3·5 mm.) and thus different percentage values and nuclear configurations at the posterior commissure level. The larger percentage values exhibited the more anterior characteristics.

Vertical.—In the vertical plane the position of the posterior commissure (and therefore that of the "O" horizontal plane) with respect to the thalamic nuclei was also subject to variation. The distance from the "O" horizontal plane to the lower (X) and the upper (Y) border of the thalamus (Fig. 1b) were measured at the posterior commissure level in the three groups of brains described above. The ratio Y/X was recorded and also the total thalamic height (X + Y).

	X	Y	X + Y	Y/X
Group 1	0 – 4 mm.	12·0 – 16·5	12·5 – 17·75	3·2 – 33·0
Group 2	1 – 4 mm.	13·0 – 17·5	15·0 – 20·5	3·2 – 12·0
Group 3	1 – 5 mm.	11·5 – 18·0	13·5 – 19·5	2·6 – 14·2

Relations of the Mid-thalamic Point

The position of the mid-point of the line between the interventricular foramen and the posterior commissure varied between 60·5 and 70% of the total thalamic length measured from the pulvinar.

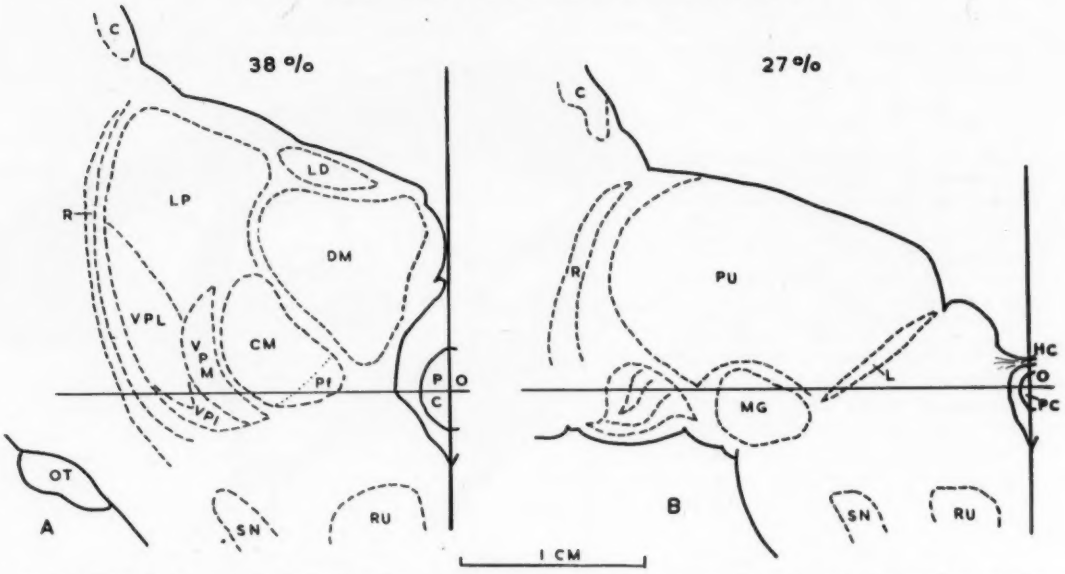

FIG. 2.—Disparity between the thalamic nuclear configuration at the posterior commissure level in two hemispheres with percentage values (of posterior commissure) of (A) 38 and of (B) 27.

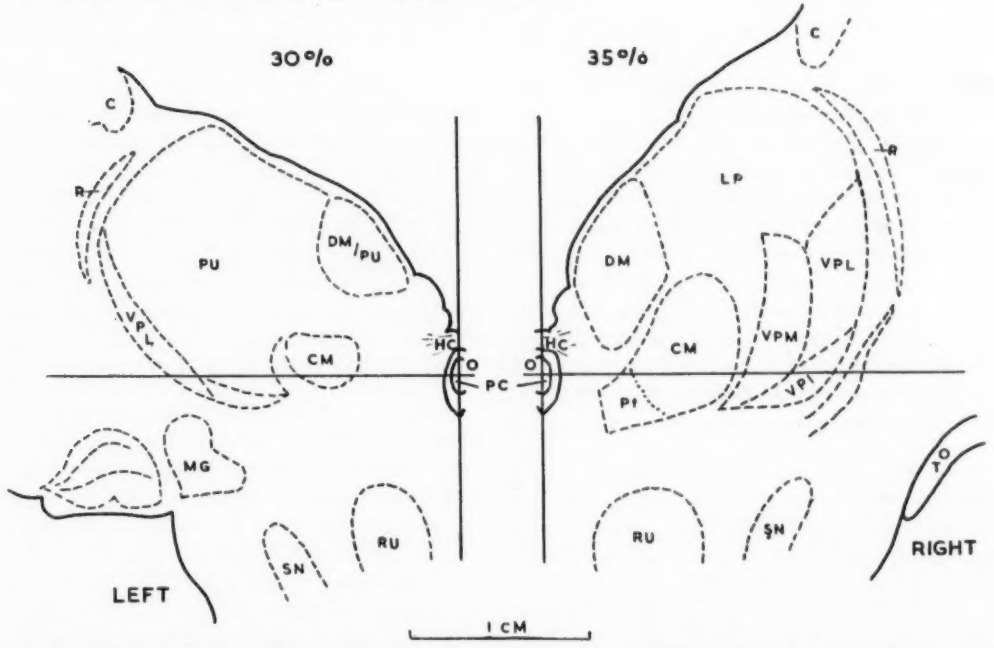

FIG. 3.—Disparity between the thalamic nuclear configuration at posterior commissure level in one brain. The ventricular length is equal (24 mm.) but the total thalamic length is unequal (left 30 mm., right 37 mm.).

A	=	Nucleus anterior thalami
AC	=	Commissura anterior
AM	=	Amygdala
C	=	Nucleus caudatus
CC	=	Corpus callosum
CM	=	Nucleus centrum medianum
DM	=	Nucleus medialis dorsalis thalami
F	=	Fornix
Gl.P	=	Globus pallidus
HC	=	Commissura habenularis
LD	=	Nucleus lateralis dorsalis thalami
LG	=	Corpus geniculatum lateralis
LP	=	Nucleus lateralis posterior thalami
MG	=	Corpus geniculatum medialis
MM	=	Nucleus mammillaris medialis
Mth	=	Tractus mammillo-thalamicus
OT	=	Tractus opticus
PC	=	Commissura posterior
Pf	=	Nucleus parafascicularis
PN	=	Pineal
PU	=	Pulvinar
PUT	=	Putamen
R	=	Nucleus reticularis
RU	=	Nucleus ruber
Sb	=	Nucleus subthalamicus
SN	=	Substantia nigra
VA	=	Nucleus ventralis anterior thalami
VL	=	Nucleus ventralis lateralis thalami
VPI	=	Nucleus ventralis postero-inferior thalami
VPL	=	Nucleus ventralis postero-lateralis thalami
VPM	=	Nucleus ventralis postero-medialis thalami

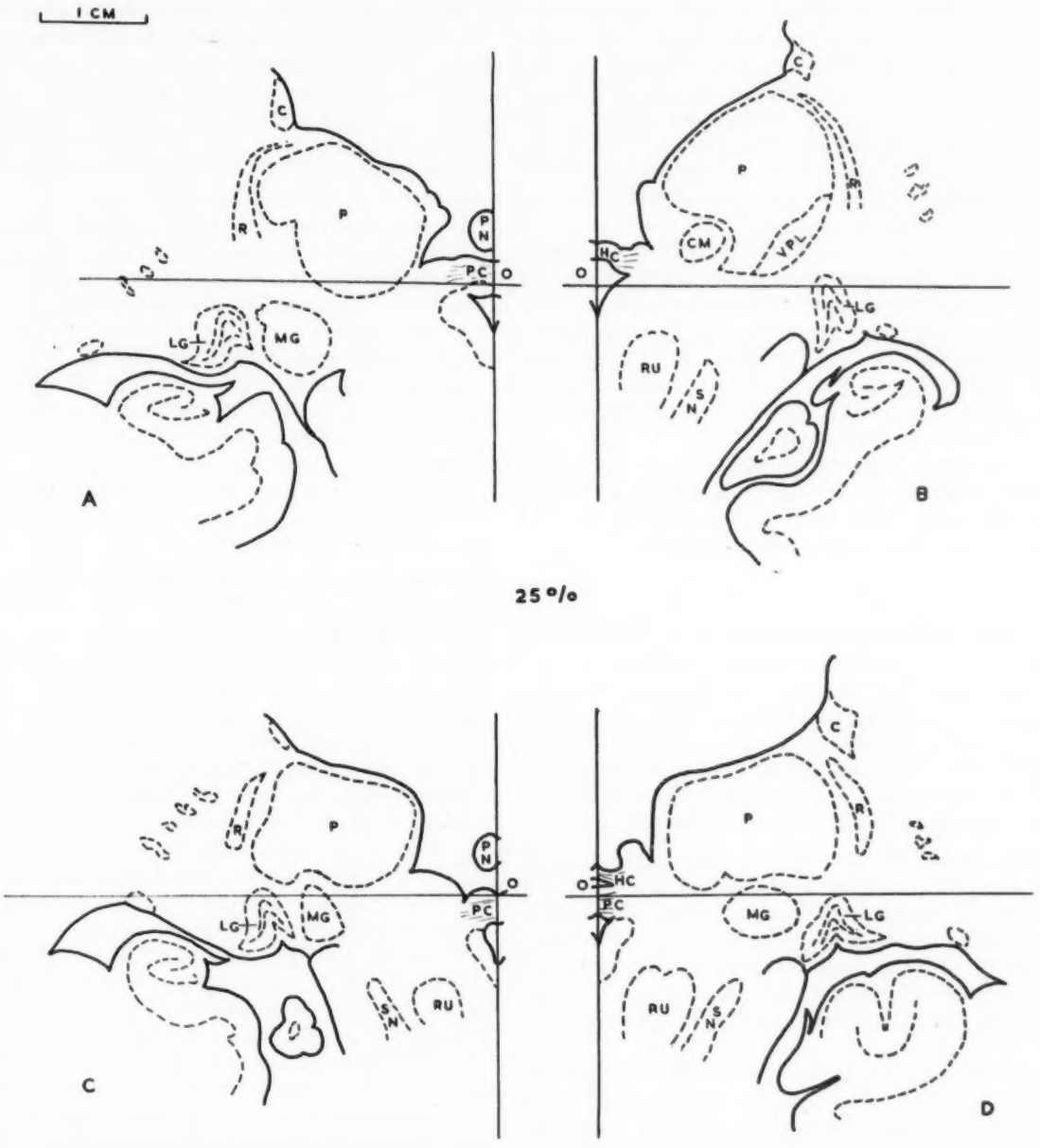

FIG. 4.—Typical and closely similar thalamic nuclear configuration at 25% of the total thalamic length measured from the pulvinar. The percentage values of the anterior curvature of the posterior commissure were A = 40, B = 23, C = 36, D = 28.

A	=	Nucleus anterior thalami
AC	=	Commissura anterior
AM	=	Amygdala
C	=	Nucleus caudatus
CC	=	Corpus callosum
CM	=	Nucleus centrum medianum
DM	=	Nucleus medialis dorsalis thalami
F	=	Fornix
Gl.P	=	Globus pallidus
HC	=	Commissura habenularis
LD	=	Nucleus lateralis dorsalis thalami
LG	=	Corpus geniculatum lateralis
LP	=	Nucleus lateralis posterior thalami
MG	=	Corpus geniculatum medialis
MM	=	Nucleus mammillaris medialis
Mth	=	Tractus mammillo-thalamicus
OT	=	Tractus opticus
PC	=	Commissura posterior
Pf	=	Nucleus parafascicularis
PN	=	Pineal
PU	=	Pulvinar
PUT	=	Putamen
R	=	Nucleus reticularis
RU	=	Nucleus ruber
Sb	=	Nucleus subthalamicus
SN	=	Substantia nigra
VA	=	Nucleus ventralis anterior thalami
VL	=	Nucleus ventralis lateralis thalami
VPI	=	Nucleus ventralis postero-inferior thalami
VPL	=	Nucleus ventralis postero-lateralis thalami
VPM	=	Nucleus ventralis postero-medialis thalami

This represented a distance of about 3·3 mm. in a brain of average total thalamic length (34·5 mm.). The variation in nuclear pattern between the two extremes was not great. The dorsomedial and ventrolateral nuclei were seen in all cases, while at the anterior limit of variation the posterior end of the anterior complex was seen. At the posterior limit, the nucleus lateralis dorsalis was present and the anterior complex was absent.

In the vertical plane "X" varied from 0 to 5·5 mm. and in two cases the lower border of the thalamus lay 2·0 mm. above the "O" horizontal plane. The distance "Y" varied from 11·0 to 17·5 mm., total thalamic height (X + Y) from 14·0 to 21·0 mm. and the ratio Y/X from 2·3 to 12·4, indicating the inconstancy of the level at which the "O" horizontal plane intersects the thalamus.

It was noted that a broad relationship was demonstrable when the total thalamic height (X + Y) was plotted against brain weight. The range of (X + Y) for any one brain weight was ± 2·0 mm.

RESULTS IN PART II

Antero-posterior Organization in the Thalamus

In this series of 13 hemispheres the distance "V" varied from 21 to 26 mm. and the total thalamic length "T" from 30·5 to 38·0 mm. The distance from the posterior commissure to the tip of the pulvinar equals 23 to 40% of the total thalamic length. In all but one case (23%) the posterior commissure lay a variable distance in front of the 25% level.

25% Level (Fig. 4).—The pulvinar was seen in all 13 hemispheres, the full development of both geniculate bodies appeared in nine, the lateral geniculate in three, and neither in one. The extreme posterior tip of the centromedian nucleus appeared in four specimens and the posterior end of the ventralis posterolateralis and posteromedialis in three.

At the anterior limit of variation the posterior ends of VPM, VPL, and the centromedian were present (Fig. 4B), whereas the pulvinar alone was seen at the posterior limit (Figs. 4A, C, D). The distance between these two extremes would be about 1·5 mm. in an average total thalamic length of 34·5 mm.

In all but one case a variable portion of the posterior commissure and periaqueductal grey matter were displayed at this level.

In the vertical plane "X" varied from 0 to 3·0 mm. In five cases the lower border of the thalamus lay up to 3·0 mm. above the "O" horizontal plane. "Y" varied from 13 to 19 mm., the total thalamic height from 12 to 18·5 mm., and the ratio Y/X from 4 to 12·5.

50% Level (Fig. 5).—At this level the anterior tip of VPM, VPL, and the centromedian nucleus were seen. The fully developed dorsomedial nucleus lay medially, the lateralis posterior laterally, and the lateralis dorsalis dorsally. Antero-posterior variation at this level involved only a narrow band at the anterior end of VPM, VPL, and CM representing a distance of about 1·5 mm.

Globus Pallidus.—The cross sectional areas and configuration were closely comparable throughout. The medial edge of this structure lay between 13 and 24 mm. and the lateral border between 24 and 29 mm. from the midline. The lower border lay from 2 to 9 mm. below the horizontal zero plane.

In the hypothalamic region the 50% coronal plane passed through the posterior parts of the mammillary bodies in three brains and lay posterior to them in the remaining ten.

In the vertical plane "X" varied from 0 to 4·5 mm., "Y" from 15 to 21 mm., (X + Y) from 17 to 22 mm., and the ratio Y/X from 4 to 23.

75% Level (Fig. 5).—At this level the ventralis lateralis, the ventralis anterior, and the anterior part of the dorsomedial nuclei were seen. The anterior complex was fully developed in all cases. The extent of antero-posterior variation in the thalamus at this level was very small and probably less than a millimetre. The mammillo-thalamic tract (bundle of Vicq d'Azyr) appeared in 11 brains.

Globus Pallidus.—The cross sectional areas and internal configuration were again closely similar at this level. The medial edge lay between 12 and 19 mm. and the lateral edge between 22 and 32 mm. from the midline. The lower border lay from 2 to 9 mm. below the horizontal zero plane.

Ventrally, the 75% coronal plane passed through the middle of the mammillary bodies in the two brains, through their anterior portions in two, and through the tuberal region in nine.

In the vertical plane "X" varied from 0 to 5·0 mm. and in three instances lay up to 1 mm. above the "O" horizontal plane. "Y" varied from 12 to 20 mm., total thalamic height (X + Y) from 15·5 to 21·0 mm., and the ratio Y/X from 2·5 to 10.

100% Level (Fig. 5).—This lay anterior to the thalamus and presented only the internal capsule (anterior limb) and the anterior portion of the corpus striatum.

Globus Pallidus.—Only the outer segment was seen at this level in all cases. Its lateral border lay between 15 and 23 mm. from the midline and its lower border between 4 and 10 mm. below the "O" horizontal plane. The medial edge of the pallidum was too ill-defined macroscopically to permit of measurement.

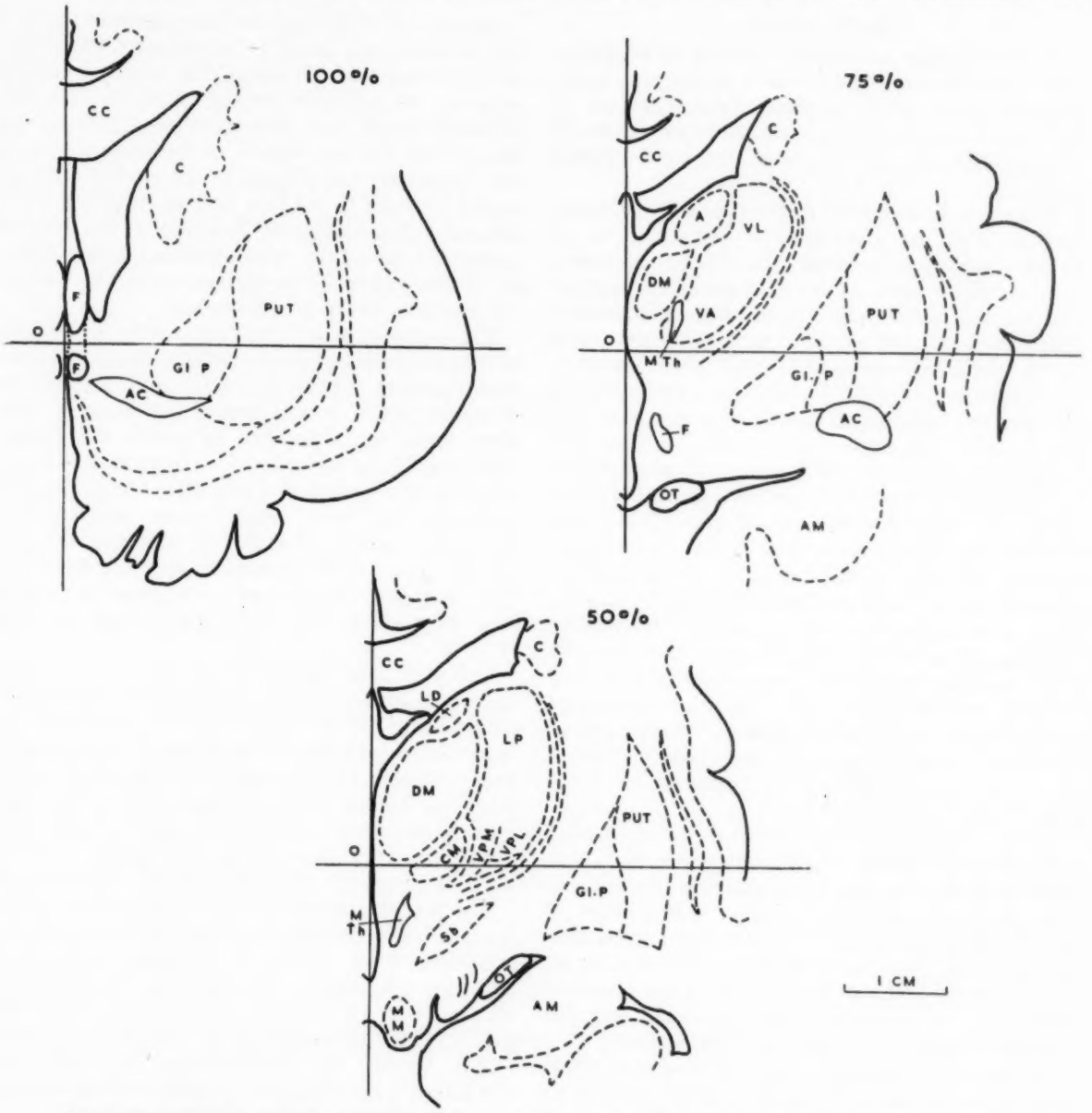

FIG. 5.—Typical nuclear configuration at 100, 75, and 50% levels of the total thalamic length measured from the pulvinar.

A	=	Nucleus anterior thalami
AC	=	Commissura anterior
AM	=	Amygdala
C	=	Nucleus caudatus
CC	=	Corpus callosum
CM	=	Nucleus centrum medianum
DM	=	Nucleus medialis dorsalis thalami
F	=	Fornix
Gl.P	=	Globus pallidus
HC	=	Commissura habenularis
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LG	=	Corpus geniculatum lateralis
LP	=	Nucleus lateralis posterior thalami
MG	=	Corpus geniculatum medialis
MM	=	Nucleus mammillaris medialis
Mth	=	Tractus mammillo-thalamicus
OT	=	Tractus opticus
PC	=	Commissura posterior
Pf	=	Nucleus parafascicularis
PN	=	Pineal
PU	=	Pulvinar
PUT	=	Putamen
R	=	Nucleus reticularis
RU	=	Nucleus ruber
Sb	=	Nucleus subthalamicus
SN	=	Substantia nigra
VA	=	Nucleus ventralis anterior thalami
VL	=	Nucleus ventralis lateralis thalami
VPI	=	Nucleus ventralis postero-inferior thalami
VPL	=	Nucleus ventralis postero-lateralis thalami
VPM	=	Nucleus ventralis postero-medialis thalami

DISCUSSION

It should again be stressed that this investigation was undertaken not to provide a stereotactic reference atlas but solely to assess the importance of individual variation in so far as it concerns spatial relationships in the diencephalon and globus pallidus.

In any study of spatial relationships in the brain, consideration of post-mortem distortion is of primary importance. In the human brain this factor is unavoidable since, in the absence of the support and volume of the pulsating vascular tree, cerebral dimensions will be reduced to an unknown and variable extent (Mark and Yakovlev, 1955). Further, the cerebrospinal fluid, in which the brain almost floats *in vivo*, disappears rapidly after death causing the brain to sink upon the subjacent cranium with consequent distortion. Perfusion *in situ* as employed by Spiegel and Wycis (1952) and by Talairach, David, Tournoux, Corredor, and Kvasina (1957) will not correct this factor as evidenced by the unequal spacing of the initially parallel guide needles inserted into the fresh specimen by the latter authors. Thus there appeared to be no greater objection to making use of brains removed as soon as possible after death and suspended (by the basilar artery) in a large volume of fixative. In such specimens furthermore, the range of thalamic length (20·0 to 26·0 mm.) is similar to that encountered in a series of 14 normal encephalograms corrected for *x*-ray magnification (22·5 to 26·0 mm.).

Again, the variation in the position of the posterior commissure, together with the existence of a proportionate arrangement of the thalamic nuclei along the total thalamic length suggest that neither of these findings could be attributed to distortion consequent upon fixation. Individual variation is therefore the most probable explanation of the observed differences in both the antero-posterior and the vertical relations of the posterior commissure.

In the antero-posterior axis, the posterior commissure lay between 26 and 41% (first series of 40 brains) and 23 and 40% (second series of 13 brains) of the total thalamic length measured from the tip of the pulvinar. The underlying thalamic nuclear pattern was seen to become more posterior in character the further caudalwards the posterior commissure lay along the thalamic axis (Figs. 2 and 6). Cases with identical "ventricular lengths" (22 mm.) but different percentage values for the posterior commissure (29 to 38) showed correspondingly different nuclear patterns at this level (Fig. 6). On the other hand, cases with similar percentage values for the posterior commissure (36 to 37) and different ventricular lengths (20·5 to 24·0 mm.) presented almost identical nuclear patterns (Fig. 7).

Spiegel and Wycis had already noted variability in the position of the posterior commissure, its distance from the posterior border of the lateral geniculate body or the pulvinar varying by up to 3·0 mm. Similarly Mark and Yakovlev found that the distance from the commissure to the posterior tip of the "posteromedial portion of the ventral nucleus" varied from 2·1 to 7·2 mm. in a series of five hemispheres. The finding of Talairach *et al.* that the posterior edge of the centromedian nucleus always lay at the level of the posterior commissure was not confirmed in the present material.

The existence of left-right asymmetry in the position of diencephalic nuclei was described by Delmas and Pertuiset (1954) but was not observed by Talairach *et al.* In the present investigation there were three brains in each of which the nuclear configuration at the posterior commissure differed considerably between the two sides. While in each brain the ventricular lengths were closely similar, the total thalamic lengths and therefore the percentage values of the posterior commissure differed. The more posterior nuclear configuration was to be seen on the side with the lower percentage value (Fig. 3).

The additional variability of the posterior commissure in the vertical plane follows from the demonstration that the zero horizontal plane through the commissure intersects the thalamus at an inconstant level. Thus in the first series, the ratio X/Y varied from 2·6 to 33·0 at the coronal level of the commissure and from 2·3 to 12·4 at mid-thalamic level. Similar variation in this ratio was noted at each of the four coronal planes studied in the second series.

The practical implication of these findings is that the posterior commissure should not be used as a landmark from which to measure the antero-posterior coordinates of nuclei in the thalamus. This consideration will be of particular importance for such small structures as the sensory relay nuclei (VPL, VPM), the centromedian, and the subthalamic nuclei, where the proximity to the internal capsule makes maximum accuracy desirable.

For the antero-posterior coordinate it seems that greater accuracy could be attained by making use of the fact that the thalamic nuclei appear to occupy relatively constant proportions of the total thalamic length as suggested by the findings in the second series. The total thalamic length can be estimated in an air encephalogram in which the line from the anterior commissure or interventricular foramen to the posterior commissure is prolonged backwards to intersect the surface of the pulvinar as visualized with air in the cisterna ambiens. The antero-posterior correction factor would then be the ratio between this length in the patient's brain (corrected

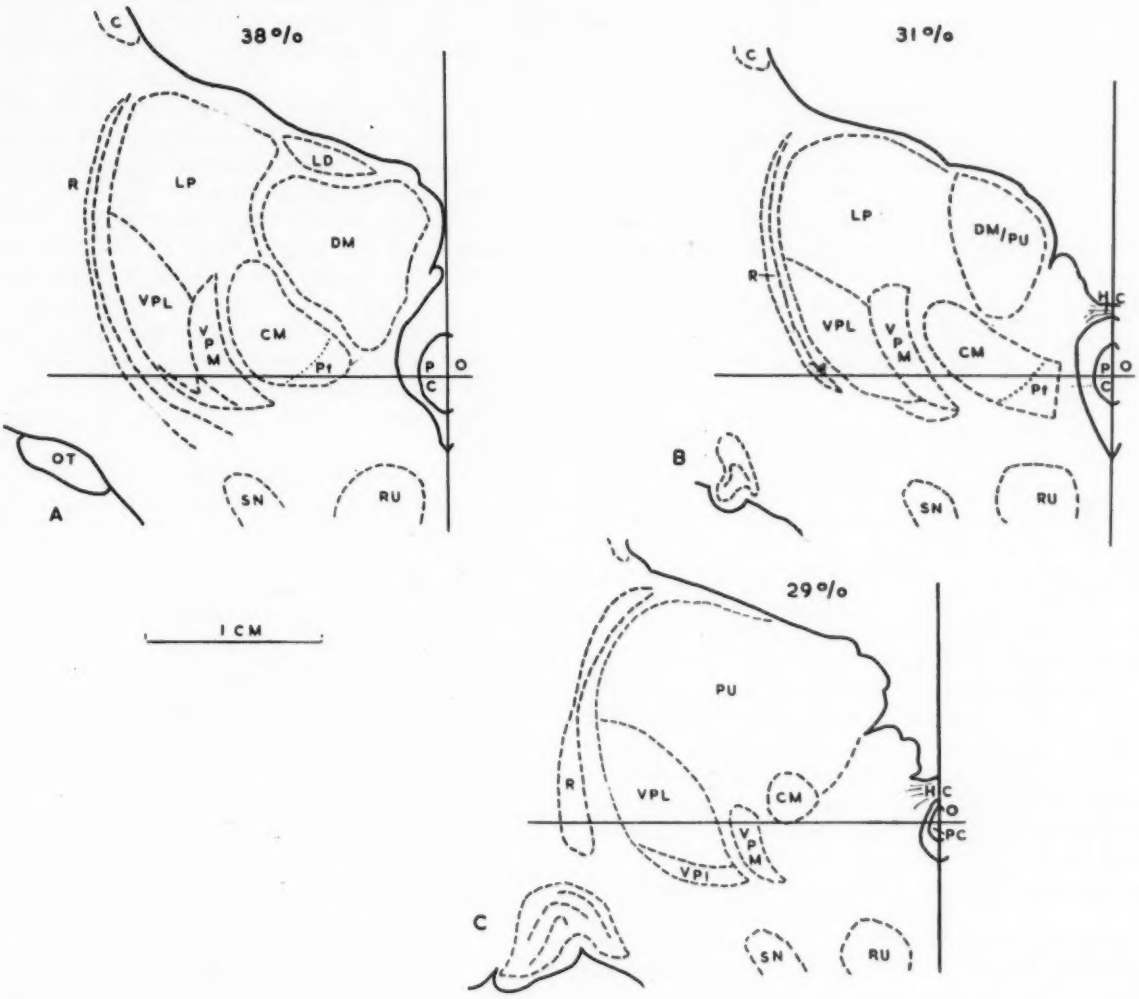

FIG. 6.—Disparity between the thalamic nuclear configuration at the posterior commissure level in three hemispheres of identical ventricular length (22 mm.) but different percentage values (38, 31, and 29).

A	=	Nucleus anterior thalami
AC	=	Commissura anterior
AM	=	Amygdala
C	=	Nucleus caudatus
CC	=	Corpus callosum
CM	=	Nucleus centrum medianum
DM	=	Nucleus medialis dorsalis thalami
F	=	Fornix
Gl.P	=	Globus pallidus
HC	=	Commissura habenularis
LD	=	Nucleus lateralis dorsalis thalami
LG	=	Corpus geniculatum lateralis
LP	=	Nucleus lateralis posterior thalami
MG	=	Corpus geniculatum medialis
MM	=	Nucleus mammillaris medialis
Mth	=	Tractus mammillo-thalamicus
OT	=	Tractus opticus
PC	=	Commissura posterior
Pf	=	Nucleus parafascicularis
PN	=	Pineal
PU	=	Pulvinar
PUT	=	Putamen
R	=	Nucleus reticularis
RU	=	Nucleus ruber
Sb	=	Nucleus subthalamicus
SN	=	Substantia nigra
VA	=	Nucleus ventralis anterior thalami
VL	=	Nucleus ventralis lateralis thalami
VPI	=	Nucleus ventralis postero-inferior thalami
VPL	=	Nucleus ventralis postero-lateralis thalami
VPM	=	Nucleus ventralis postero-medialis thalami

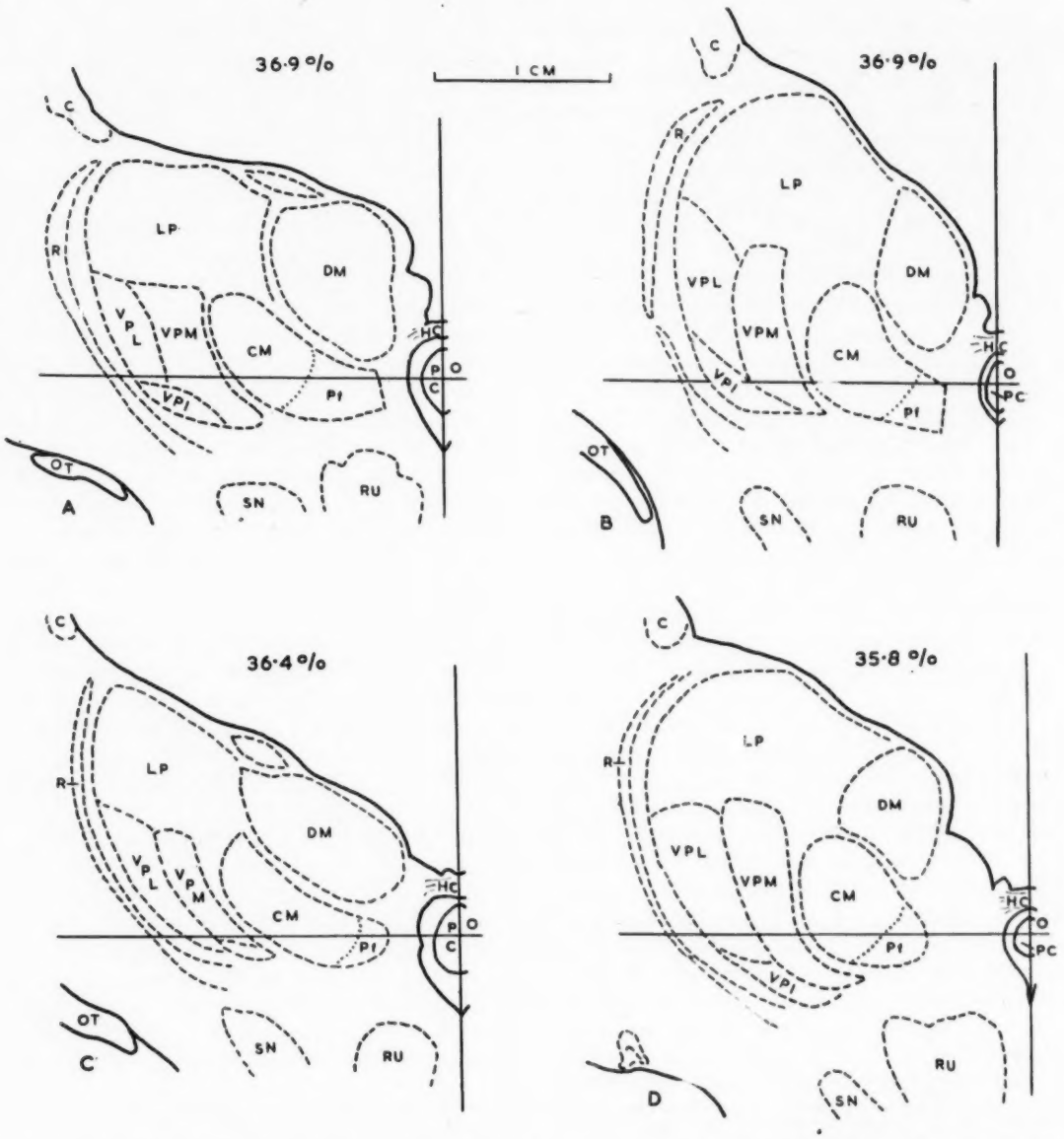

FIG. 7.—Similar thalamic nuclear configuration at the posterior commissure level in four hemispheres with closely similar percentage values (36 to 37) but different ventricular length (20 to 24).

A	=	Nucleus anterior thalami
AC	=	Commissura anterior
AM	=	Amygdala
C	=	Nucleus caudatus
CC	=	Corpus callosum
CM	=	Nucleus centrum medianum
DM	=	Nucleus medialis dorsalis thalami
F	=	Fornix
Gl.P	=	Globus pallidus
HC	=	Commissura habenularis
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VA	=	Nucleus ventralis anterior thalami
VL	=	Nucleus ventralis lateralis thalami
VPI	=	Nucleus ventralis postero-inferior thalami
VPL	=	Nucleus ventralis postero-lateralis thalami
VPM	=	Nucleus ventralis postero-medialis thalami

or *x*-ray magnification) and the same distance in he brain from which the stereotactic atlas had been prepared. Such an atlas should also indicate the proportion of the total thalamic length occupied by the target nucleus.

For the vertical coordinate, however, it is clear hat the only valid correction factor would be one elating the total thalamic heights in the atlas and patients' brains. It is clearly impossible, however, o know the position of the lower border of the thalamus and thus its total height. In the absence of nformation concerning the extent of the patient's halamus below the horizontal plane (X), a ratio between its height above the horizontal plane (Y) in atlas and patients' brains as employed, for example, by Riechert and Hassler (1955), cannot constitute a correction factor valid for every case.

For the lateral coordinate, a correction factor is also required and Riechert and Hassler have made use of the ratio between the thalamic breadths in the atlas and the patients' brains. This dimension is measured in the antero-posterior encephalogram as the horizontal distance between the septum pellucidum and a perpendicular through the upper and outer angle of the lateral ventricle. That this latter line is not a reliable index of the outer border of the thalamus was shown by Talairach *et al.* who concluded that there was no single "lateral" correction factor valid for all cases. It was suggested that for any one nucleus a value should be employed representing the mean of its coordinates as determined in anatomical studies. The findings of the present investigation are in support of these conclusions.

Limits of Accuracy

When the best available correction factor has been applied to each of the three coordinates an attempt must be made to answer the question, What are the limits of accuracy of which the stereotactic technique is capable? It is clear that three groups of factors are relevant:—

(1) Distortion during Fixation and Processing.—This factor concerns the preparation of the "atlas brain". It should at once be emphasized that the dimensions *in vivo* of this brain, including "ventricular" and "total thalamic" lengths, cannot be known. The additional unavoidable distortion occurring after death and during fixation and processing has already been discussed.

(2) Individual Variation.—Reasons for the rejection of the posterior commissure as a reference point for antero-posterior measurements in the thalamus have been presented. Even if use is made, as suggested, of the relative constancy of the position of nuclei along the total thalamic length, it is believed that accuracy cannot be better than $\pm$ 0·75 mm. in the zero horizontal plane and will be poorer for points above or below it.

In the vertical direction, however, the problem of variation would appear to be insuperable and at least as far as the thalamus is concerned vertical accuracy will range from $\pm$ 2·5 to 3·5 mm. according to the antero-posterior level.

The appearances of the globus pallidus at the 100, 75, and 50% thalamic levels show little variation, suggesting that its antero-posterior disposition may parallel that of the thalamus. In the vertical and lateral directions variation is considerable and would appear to be random.

(3) Instrumental.—The use of radiographic control as, for example, by Hassler and Riechert (1954) and Leksell (1949), ensures that the position of the needle tip shall be exactly that calculated from the stereotactic atlas after application of the appropriate correction factors. In this way instrumental error can be reduced to negligible proportions.

It will thus be apparent that the accuracy of the stereotactic technique in the human brain will be determined not by the mechanical precision of a particular instrument but by the unavoidable shortcomings of every atlas and by our limited ability to assess and to correct for the major factor of individual variation. It is to be emphasized that studies of the latter should be based not only on an adequate number of specimens but also upon histological investigations which alone can reliably define the boundaries of diencephalic nuclei.

In conclusion, a coordinate system based upon a horizontal plane through the posterior commissure has been shown to be subject to the variability of the position of the latter (in antero-posterior and vertical directions). Nevertheless it seems unlikely that any more satisfactory plane can be defined for the diencephalon on the basis of structures identifiable in an encephalogram of the third ventricle. The present writers are therefore of the opinion that the future of the stereotactic technique probably lies in the direction of the development of physiological methods which will permit the exploration of nuclei and fibre systems with minimal trauma until the target is reached as judged by physiological criteria. The role of the three-coordinate system (using optimal corrections for individual variation) would then be to define the minimal volume of tissue to be explored.*

*The authors regret that they have been unable to gain access to a copy of "Introduction to Stereotaxis with an Atlas of the Human Brain" by G. Schaltenbrand and P. Bailey (1958).

SUMMARY

Wide individual variation in the antero-posterior and vertical position of the posterior commissure was demonstrated in a histological investigation of 40 hemispheres.

The posterior commissure was found to bear no constant relationship to the thalamic nuclei in the antero-posterior or vertical plane.

The antero-posterior range of the position of the posterior commissure was from 26 to 41% of the total thalamic length. This difference represented 5·3 mm. in an average total thalamic length of 34·5 mm.

In the vertical plane the position of the posterior commissure varied by up to 6·5 mm. with respect to the upper surface of the thalamus.

A proportionate arrangement of the thalamic nuclei in the antero-posterior axis was demonstrated in all 53 hemispheres.

A less inexact method was suggested for the determination of the antero-posterior coordinate of a thalamic nucleus. No comparable method appeared feasible for the vertical coordinate.

Considerable variation was demonstrated in the lateral and vertical coordinates of the globus pallidus

Limitations of accuracy in human stereotacti brain surgery were discussed, the paramoun importance of individual variation being stressed.

We are indebted to Dr. R. D. Hoare, consultan neuroradiologist to the Guy's-Maudsley Neurosurgica Unit, for permission to make use of the series o encephalograms.

REFERENCES

Brierley, J. B., and Beck, E. (1957). Proc. 1st Int. Congr. neurol. Sciences. (6th Int. Congr. Neurol.) Brussels, *Excerpta Med. (Amst.)*, 38-39, Sect. VIII, **70**, Suppl. (Congress issue).

Delmas, A., and Pertuiset, B. (1954). *Presse méd.*, **62**, 458.

Hassler, R., and Riechert, T. (1954). *Nervenartz.*, **25**, 441.

Horsley, V., and Clarke, R. H. (1908). *Brain*, **31**, 45.

Leksell, L. (1949). *Acta chir. scand.*, **99**, 229.

Loewenfeld, I. E., and Altman, R. (1956). *J. Neuropath. exp. Neurol.*, **15**, 181.

Mark, V. H., and Yakovlev, P. I. (1955). *Anat. Rec.*, **121**, 745.

Olszewski, J. (1951). *Ibid.*, **109**, 332.

Riechert, T., and Hassler, R. (1955). Personal communication.

Spiegel, E. A., and Wycis, H. T. (1952). Stereoencephalotomy (Thalamotomy and Related Procedures). Part I. *Methods and Stereotaxic Atlas of the Human Brain*, p. 38. Grune and Stratton, New York.

——, ——, Marks, M. and Lee, A. J. (1947). *Science*, **106**, 349.

Talairach, J., Ajuriaguerra, J. de, and David, M. (1952). *Presse méd.*, **60**, 605.

——, David, M. Tournoux, P., Corredor, H., and Kvasina, T. (1957). *Atlas d'Anatomie Stéréotaxique*. Masson, Paris.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 299.

SENSORY, MOTOR, AND REFLEX CHANGES IN TWO CASES OF INTRACTABLE PAIN AFTER STEREOTACTIC MESENCEPHALIC TRACTOTOMY

BY

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Section of the spino- and trigeminothalamic fibres at the level of the mesencephalon for intractable pain was first performed by Dogliotti (1938). A few years later Walker (1942a) developed a standard technique for section of the pain fibres at the level of the posterior margin of the superior colliculus, and later several cases of mesencephalic tractotomy were published (Guiot and Forjaz, 1947; David, Talairach, and Hécaen, 1947; Sjöquist, 1949; Walker, 1950; Schwartz, 1950; White and Sweet, 1955). Since this procedure involves a somewhat high mortality, attempts have been made at the Neurosurgical Clinic in Lund to destroy the spinothalamic tract at mesencephalic levels by stereotactic methods. So far the operation has been tried in only a few cases. The present report represents an analysis of the neurological and necropsy findings in two patients.

Both cases presented were operated upon by Professor Leksell in Lund. The technique and apparatus employed have been described elsewhere (Leksell, 1957), and will only be briefly commented upon below.

Case Reports

Case 1.—The patient was a 19-year-old girl suffering from cancer in the right lung. Her pulmonary symptoms started in June, 1956, and at the time the diagnosis was confirmed the tumour was considered inoperable. She was admitted to the Neurosurgical Clinic in Lund, Sweden, on December 14, 1956, because of unbearable pain in the right upper extremity and the right half of the chest. The pain was considered to be due to metastases with pressure on the right brachial plexus and intercostal nerves, and it was decided to perform a left-sided mesencephalic tractotomy.

Pre-operative Neurological Examination.—In addition to the spontaneous pain, she complained of intense cutaneous hyperaesthesia in the right upper extremity and right side of the chest. There was a slight hypoaesthesia to pinprick within the same area, but no sensory loss in the rest of the body. Muscle-joint sensation and stereognosis were normal. The right upper extremity showed some diffuse muscular atrophy and was somewhat weaker than the left. These symptoms were probably in part due to inactivity caused by the hyperaesthesia. There were no pareses of the other extremities, and movements were rapidly and precisely performed in all limbs. The abdominal, plantar, and tendon reflexes were normal. Examination of the cranial nerves did not reveal any abnormalities.

Operation.—The operation was performed under local anaesthesia on December 21, 1956. The stereotactic apparatus developed by Leksell (1957) was used, and the lesion was produced by bipolar thermocoagulation to 52°C. The electrodes were introduced through a small burr hole in the left parieto-occipital region with the mesencephalic aqueduct and posterior commissure as reference points. Stimulation of both electrodes before the coagulation produced a sensation of pain in the entire right half of the body, and the operation resulted in subtotal analgesia in the right half of the body. No detailed neurological examination was made immediately after the operation.

Post-operative Course.—The patient recovered from the operation within a few days. Her general condition improved considerably, and she got out of bed and started walking a little. She still felt slight pain in the right side of the chest and arm, but it was insignificant compared with the pre-operative state, and the dose of analgesics was reduced to a minimum. However, six weeks after the operation she again gradually got worse, with increasing dyspnoea and emaciation. She now had severe pain in the left side of the chest, and gradually also in the right side. There was no certain increase of the pain in the right arm, and the pain in the right side of the chest was considerably less than on the left. The dose of analgesics again reached the pre-operative level. During the last weeks it was difficult to obtain reliable information concerning the intensity of the pain on the two sides. She died from increasing respiratory distress and general emaciation on March 9, 1957, two and a half months after the operation.

Post-operative Neurological Examinations.—The first complete neurological examination was performed four days after the operation. She was then analgesic to pinprick on the right arm and leg (Fig. 1) but strong pinching of the skin evoked a diffuse disagreeable feeling

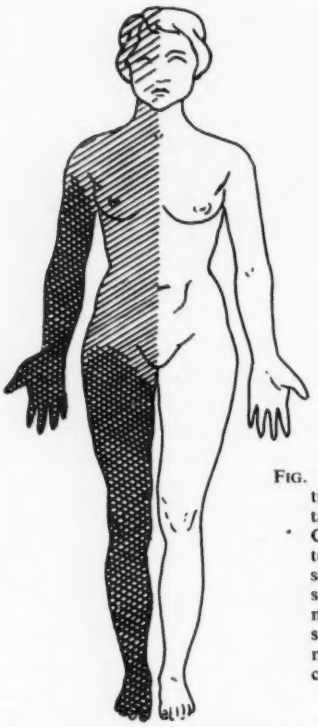

FIG. 1.—Diagram showing the distribution of the preserved cutaneous sensation in Case 1. Cross-hatchings indicate subtotal anaesthesia, hatched areas somewhat better preserved sensation for all cutaneous sensory modalities. The best preserved sensation was found around the mouth and within the buccal cavity.

which spread to most of the extremity. The same paraesthesiae were produced by vibration from a tuning fork. In the right half of the trunk there was a slight, but distinct pain reaction to pinprick, which was fairly well localized. The same degree of hypoalgesia was found in the right half of the forehead, while the sensation was somewhat better preserved on the chin. Around the mouth and lips and in the right half of the buccal cavity and tongue, there was a rather strong reaction to pain precisely localized. The best preserved pain sensitivity was found within the mouth. A similar distribution was found for preserved temperature and touch. Strong warm and cold stimuli were seldom correctly perceived on the right arm and leg, while temperature differences were rather well differentiated on the trunk and particularly in and around the mouth. Touch stimuli were frequently felt on the right arm and leg, but very poorly localized. On the trunk light touch stimuli were perceived and more precisely localized while the best preservation was found within the buccal cavity (Fig. 1). Muscle-joint sensitivity was very poor. She could sometimes localize movements in the shoulder, knee, etc., but could not tell which finger or toe was moved. The taste sensation was greatly diminished on the right half of the tongue, but not abolished. On the left side of the body all sensory qualities were normal.

During the further course there was no change in the sensory status except for some increase in the paraesthesiae on pinching the skin. They could, however, only be produced by rathe intense stimuli.

From the first day after operation it was noted tha the right plantar response was extensor. On examina tion four days after the operation there was a slight paresi of the right arm and leg. The tendon reflexes wer considerably increased on the right side with clonic ankl jerk, and there was possibly also a slight increase of th left patellar and Achilles reflexes. The right abdomina reflexes were almost abolished. During the followin days the tendon reflexes on the right side grew strongl hyperactive, and there also appeared to be some increase of the left knee and ankle jerks. The strength of the right arm and leg gradually improved. One month after the operation the strength of the right arm was definitely better than pre-operatively, and there was practically no paresis of the right leg. Because of the loss of deep sensibility, finer tests for motor performance could not be made. There was no spasticity, and the strength and movements of the left extremities were normal. From the first month after the operation until death no further changes in the motor or reflex findings were observed.

Necropsy.—The whole right lung was infiltrated by a bronchial carcinoma which spread across the mediastinum and compressed the left main bronchus. Metastases were found in regional lymph nodes, the chest wall, and the right supraclavicular fossa.

The brain was fixed *in situ* by intra-arterial formalin perfusion. The spinal canal was not opened, and only the brain and the upper cervical segments of the spinal cord were removed. After further fixation in 96% alcohol the brain was cut and carefully examined. There were no signs of metastases. Nor was there any bleeding of importance along the electrode tracks. The brain-stem was cut in 15-20μ thick transverse serial sections, and every tenth section was mounted and stained with thionin to determine the extent of the lesion and for further anatomical studies. Other sections were

FIG. 2.—Photomicrograph of a Weil-stained section at the level of the lesion in Case 1.

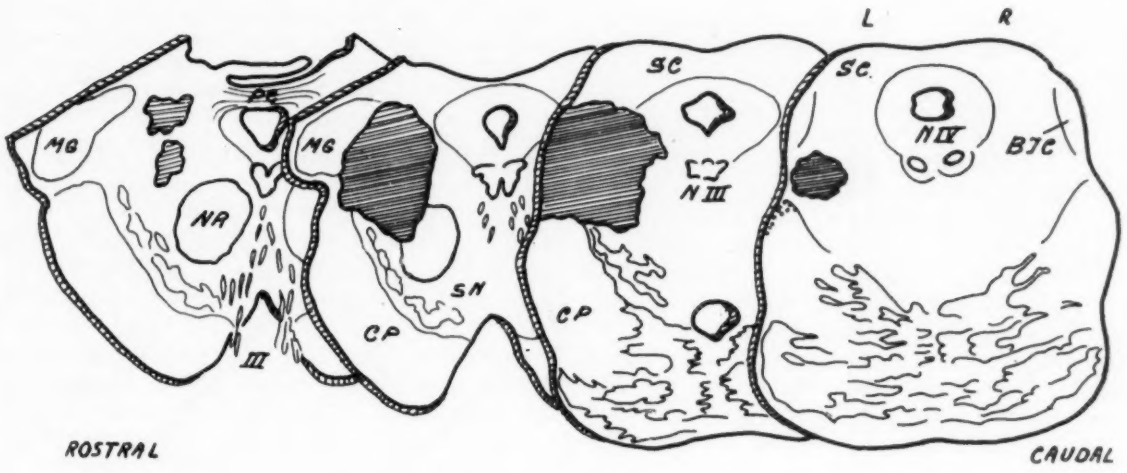

FIG. 3.—Drawings made by means of a projection apparatus showing the extent of the lesion at various levels in Case 1. The stippled area in the drawing to the right shows the localization of the degenerated fibres in the cerebral peduncle.

BIC : Brachium of inferior colliculus.
CM : Centrum medianum.
CP : Cerebral peduncle (basis pedunculi)
FMT : Mamillothalamic fasciculus.
L : Left.
MG : Medial geniculate body.
NH : Habenular nuclei.
NM : Nucleus dorsomedialis of thalamus.
NP : Nuclei of pulvinar.
NR : Nucleus ruber.
NVP : Nucleus ventralis posterior of thalamus.
N III Nucleus of oculomotor nerve.
N IV : Nucleus of trochlear nerve.
PC : Posterior commissure.
R : Right.
SC : Superior colliculus.
SN : Substantia nigra.
III : Oculomotor nerve.

stained according to the methods of Weil, Bodian, and Davenport.

The Stereotactic Lesion.—The brain-stem lesion formed a sharply circumscribed and quite regular cavity (Fig. 2), which was filled with debris and macrophages and surrounded by a thin and sparse gliotic rim. In the rostro-caudal direction the lesion extended from the level of the posterior commissure to the rostral level of the trochlear nucleus (Fig. 3). The left medial lemniscus and spinothalamic tract apparently were completely destroyed. Furthermore, there was a considerable lesion of the mesencephalic reticular formation and the brachium of the inferior colliculus, and a small part of the red nucleus and superior colliculus was also damaged. Practically no lesion was found in the basal cerebral peduncle in spite of careful examination. Only a small tip in the lateralmost part of the peduncle, measuring 2-3 mm.^{2} in cross section, was damaged (Fig. 3). The fibres from this damaged area could be followed further caudally as a tiny and sharply localized gliotic segment, which disappeared among the lateralmost parts of the pontine nuclei (Fig. 3, dotted area). Sections stained by the Bodian, Weil, or Davenport methods did not reveal any degeneration of corticospinal fibres at the level of the lesion or further caudally.

Case 2.—The patient was a 50-year-old woman. In 1944, a sarcoma of the uterus was diagnosed, and the uterus was removed. After the operation she was free from symptoms until June, 1956, when she had severe pain in the left arm radiating to the three middle fingers. Radiographs showed multiple metastases in the lungs, but no bony metastases. She was admitted to the Neurosurgical Clinic in Lund on June 18, 1956. The pain, which was considered due to pressure on the brachial plexus from metastases in the supraclavicular fossa, could not be controlled by analgesics, and it was decided to do a right-sided stereotactic mesencephalic tractotomy.

Pre-operative Neurological Examination.—There were signs of peripheral nerve lesions in the left arm and hand, with pareses and hypoaesthesia corresponding to the lower cervical segments. The left triceps reflex was abolished. No other neurological abnormalities could be detected.

Operation.—The patient was operated on on July 9, 1956, by the same technique as in the preceding case. The temperature in the centre of the lesion in this case reached 60°C. Immediately after the operation she appeared to be analgesic on the left side. However, she was rather drowsy, and no detailed examination could be made.

Post-operative Course.—She recovered rapidly from the operation and was able to walk within one week. However, she then developed rapidly increasing dyspnoea and died 14 days after the operation. She had no pain in the left arm in the post-operative period.

Post-operative Neurological Examinations.—The information available about the post-operative neurological symptoms is somewhat less exact than in the preceding

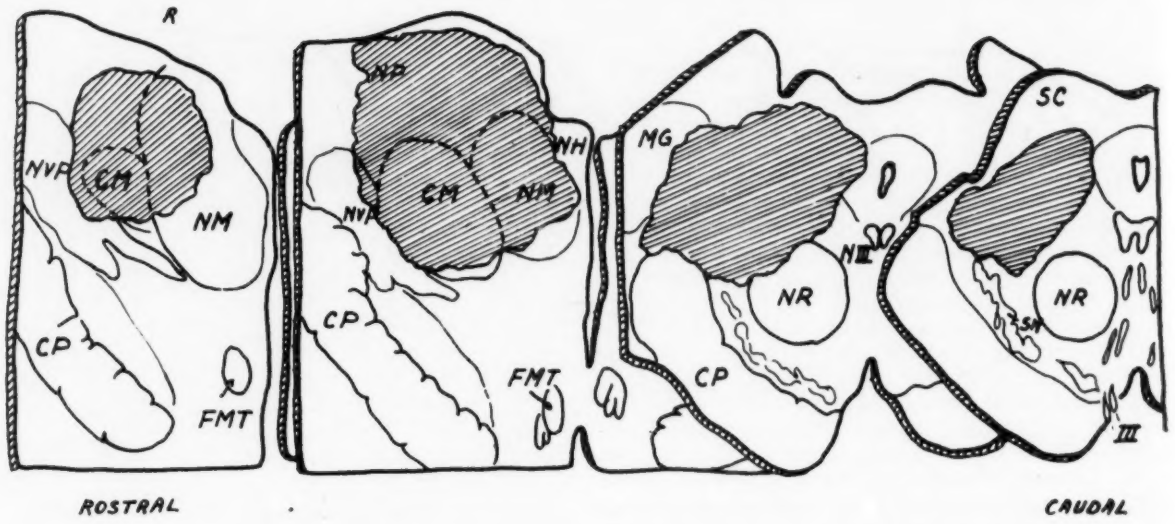

FIG. 4.—Drawings made by means of a projection apparatus showing the extent of the lesion at various levels in Case 2.

BIC :	Brachium of inferior colliculus.
CM :	Centrum medianum.
CP :	Cerebral peduncle (basis pedunculi).
FMT :	Mamillothalamic fasciculus.
L :	Left.
MG :	Medial geniculate body.
NH :	Habenular nuclei.
NM :	Nucleus dorsomedialis of thalamus.
NP :	Nuclei of pulvinar.
NR :	Nucleus ruber.
NVP :	Nucleus ventralis posterior of thalamus.
N III :	Nucleus of oculomotor nerve.
N IV :	Nucleus of trochlear nerve.
PC :	Posterior commissure.
R :	Right.
SC :	Superior colliculus.
SN :	Substantia nigra.
III :	Oculomotor nerve.

case. There was a left-sided hemi-hypalgesia to pin-prick, which did not change during the post-operative course. The hypalgesia was more marked on the extremities than on the trunk and face, and apparently it was also more marked in the distal than proximal parts of the extremities. It is stated that there was a complete left-sided hemi-anaesthesia for temperature, touch, and muscle-joint sensibility. Nothing is mentioned about post-operative paraesthesiae and reflex findings. She apparently had no pareses.

Necropsy.—Widespread metastases from the sarcoma were found in the lungs, mediastinum, and heart. The brain and upper segments of the spinal cord were removed and fixed in 10% formalin. The entire brain was cut without finding evidence of metastases. The part of the brain containing the lesion was cut in transverse serial sections and treated in the same way as described for the preceding case.

The Stereotactic Lesion.—The lesion was considerably larger and more anteriorly placed than in the preceding case, extending in a rostro-caudal direction from the habenular nuclei to the caudal end of the medial geniculate body (Fig. 4). There was considerable damage to the medial parts of the thalamus. At more caudal levels the right lemniscus medialis and spino-thalamic tract were probably completely destroyed. Also in this case the lesion was sharply delimited (Fig. 5).

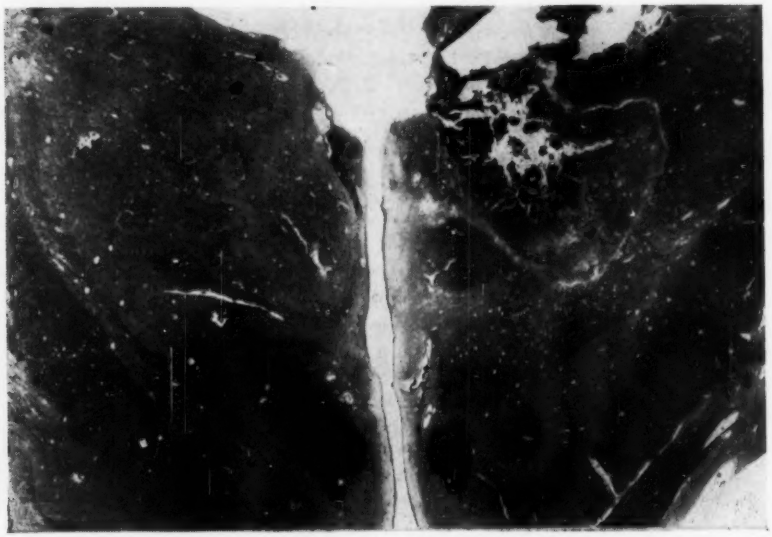

FIG. 5.—Photomicrograph of Weil-stained section at the level of the lesion in Case 2.

The central parts contained blood and necrotic tissue, surrounded by a rather dense zone of macrophages. The astroglial reaction was very slight. The greater extent of the lesion in this case was possibly in part due to an additional small haemorrhage.

Discussion

The Sensory System.—In spite of the large brain-stem lesions in the two cases reported there was a considerable amount of sensibility left on the contralateral side of the body. When attempting to explain these findings, the first point of interest is whether parts of the medial lemniscus or spinothalamic tract might have escaped destruction. At caudal mesencephalic levels the medial lemniscus and spinothalamic tract cover a rather wide area on cross section. However, they converge somewhat towards the diencephalon, and according to the present knowledge about the localization of the tracts at these levels (Walker, 1940; Rasmussen and Peyton, 1941; Riley, 1943; Glees and Bailey, 1951), there can be little doubt that they were completely severed in both cases. Since most investigators studying the localization of the tracts have employed stains visualizing medullated fibres only, it might be objected that the finest fibres may be more dispersed than the medullated ones, thus having escaped destruction in the present cases. However, fibre analyses from cross sections of the spinal cord (Häggqvist, 1936), as well as experiences with cordotomies (White and Sweet, 1955), indicate that the finest fibres of the spinothalamic tracts probably run intermingled with the myelinated ones, and a further separation of fine and coarse spinothalamic fibres above the level of the spinal cord does not appear likely. Furthermore, considering the somatotopic localization in the spinothalamic tract and medial lemniscus, the finding of equal sensory loss in the arm and leg with relatively well preserved sensory perception on the trunk in both cases does not accord with the preservation of particular segments of the spinothalamic tract or medial lemniscus.

As will be known, anatomical as well as clinical findings indicate that some of the spinothalamic fibres ascend in the spinal cord without crossing to the opposite side (Foerster and Gagel, 1933; White and Sweet, 1955), while the fibres of the medial lemniscus appear to be entirely crossed (Rasmussen and Peyton, 1948). The question then arises whether the preserved sensory perception in the present cases may be explained by transmission of sensory impulses through ipsilateral spinothalamic fibres. If this is correct, the same degree of sensory loss would be expected following mesencephalic tractotomy and cordotomy in the spinal cord. However, complete section of the anterolateral quadrant of the cord is usually followed by long-lasting contralateral analgesia, while some sensibility to pain frequently recurs shortly after mesencephalic tractotomy (White and Sweet, 1955). Furthermore, the distribution of the hypoaesthesia in the present cases, with relatively well preserved sensibility in the trunk, differs from the findings in cordotomies. It seems likely, therefore, that conduction through ipsilateral spinothalamic tract fibres cannot be the only explanation for the preserved sense perception in the cases reported.

These deliberations thus lead to the suggestion that in the brain-stem fibre systems other than the spinothalamic tract and medial lemniscus may be of importance for the perception and discrimination of sensory stimuli. From the first case described it appears that this applies to all cutaneous sensory qualities, while muscle-joint sensitivity, which was practically abolished, is probably almost entirely conveyed by the totally crossing medial lemniscus.

The number of direct spinothalamic fibres apparently is relatively small (Glees and Bailey, 1951), while numerous crossed and uncrossed spino-reticular, spino-tegmental, and spino-tectal fibres have been described (see Walker, 1940; Johnson, 1954; Rossi and Brodal, 1957; Bowsher, 1957). Similarly secondary trigemino-reticular fibres appear to be abundant (Ramón y Cajal, 1909; Scheibel, 1955; Nauta and Kuypers, 1958) Furthermore, reticulo-, tegmento-, and tectothalamic fibres have been described, particularly to the reticular and intralaminar thalamic nuclei (see Bucher and Bürgi, 1953; Johnson, 1953; Papez, 1956; Scheibel and Scheibel, 1958; Nauta and Kuypers, 1958). Admitting an extralemniscal component in the transmission of specific sensory impulses at brain-stem levels, one cannot escape considering these plurisynaptic spino- and trigeminothalamic connexions as possible pathways. Some experimental support for this view as regards sensitivity to pain has recently been given by Melzack, Stotler, and Livingston (1958). These connexions have been considered of particular importance in the transmission of diffuse pain sensations related to the so-called thalamic syndrome (Hécaen, Talairach, David, and Dell, 1949; Bowsher, 1957). On account of the convergence of different sensory modalities on single reticular neurones and the diffuse cortical spread of ascending impulses through the intralaminar and reticular thalamic nuclei, it has been considered unlikely that this system participates in the transmission of impulses leading to perception, discrimination, and recognition of sensory stimuli (French, Verzeano, and

Magoun, 1953). However, recent anatomical investigations have demonstrated reticulothalamic projections also to the specific thalamic nuclei (Scheibel and Scheibel, 1958; Nauta and Kuypers 1958), and convergence of impulses from different receptors on some of the reticular neurones scarcely excludes a more specific sensory transmission through the same system.

The contralateral facial and buccal sensitivity was particularly well preserved in the first case described, while no ipsilateral hypoaesthesia of the tongue was observed, as described by Walker (1942b). In this connexion the crossed and uncrossed dorsal trigeminothalamic tracts probably have to be considered as possible pathways of importance. It seems likely, although it cannot be proved, that the lesion in both cases also encroached upon the dorsal trigeminal tracts, while, of course, those on the opposite side remained intact. The information available about the anatomical and functional properties of these tracts is insufficient and in part contradictory (for reviews see Smyth, 1939; Walker, 1939; Russell, 1954; Berry, Anderson, and Brooks, 1956; Torvik, 1957). However, their possible role in specific sensory transmission cannot be entirely denied.

The distribution of the preserved sensitivity described in the present report (Fig. 1) is frequently encountered after cortical and thalamic lesions (Foerster, 1936; Környey, 1936). It has not been mentioned in other reports on mesencephalic tractotomy, but probably should be looked for in similar lesions. Such observations would substantiate the suggestion that in the caudal brain-stem fibre systems other than the spinothalamic tracts and medial lemnisci are involved in the specific transmission of sensory impulses of different qualities.

The Reflex Changes.—Only the first case reported permits analysis of the possible influence of the brain-stem lesion on motor function and reflex mechanisms. This patient showed considerable increase of the contralateral tendon reflexes as well as extensor plantar response and weak abdominal reflexes during the entire post-operative course. Probably there was also some increase of the tendon reflexes of the ipsilateral leg. Damage to the corticospinal fibres in the brain-stem by the lesion itself or by post-operative oedema can probably be excluded as causes for these changes. Nor was there any evidence of cerebral metastases. However, since the spinal canal was not opened, the possibility of intraspinal metastases in the cervical region has to be taken into account. The reflex changes appeared immediately after the operation, and in the following two and a half months there were no signs of progression in the neurological symptoms, except for some increase in tendon reflexes during the first weeks. Although not conclusive, this course would not be expected in intraspinal metastases from a rapidly growing tumour. The possibility thus remains that the "extrapyramidal" brain-stem lesion was responsible for the reflex changes observed, even if in current neurological thinking reflex changes of this kind have been considered almost pathognomonic of pyramidal tract lesions in man.

On the basis of animal experiments it has long been maintained that the spasticity and hyperreflexia following lesions of the internal capsule are chiefly caused by damage of extrapyramidal projection fibres (see Tower, 1949). According to Mettler (1944) and Mettler and Zimmerman (1943), the latter fibres probably cross the midline at the level of the rostral pole of the red nucleus. Conclusive human observations with regard to these problems are few, but several investigators stress the importance of pyramidal tract lesions in spasticity and hyperreflexia in man (Walshe, 1947; Lassek, 1954). However, the recent observations by Bucy (1957) that section of the corticospinal fibres at the level of the mesencephalon may give rise to only slight pareses and very little spasticity and hyperreflexia, strongly suggest an important extrapyramidal component in the production of spastic pareses also in man. From the observations of Mettler (1944) and Mettler and Zimmerman (1943), it does not appear unlikely that in the present case the lesion at the level of the red nucleus might provoke bilaterally increased tendon reflexes.

There is little doubt that pyramidal tract lesions in man and anthropoid apes usually give rise to extensor plantar response and weak or abolished abdominal reflexes (Fulton and Keller, 1932; Tower, 1949; Lassek, 1954). Less is known of whether these reflex changes may also occur following other lesions of the central nervous system. According to Lassek (1954), the Babinski sign may probably occur in man without pyramidal tract affection, and Nathan and Smith (1955) in cordotomy material found extensor plantar responses in several cases without lesions of the pyramidal tract, as well as normal plantar reflexes in cases with definite damage to corticospinal fibres. Corresponding observations apparently have not been made with regard to abdominal reflexes. However, according to the findings in the present report, it seems possible that both plantar and abdominal reflexes may be influenced by brain-stem lesions leaving the pyramidal tract intact.

Summary

Two cases with intractable pain are reported in which unilateral stereotactic brain-stem lesions were made in order to destroy the spinothalamic tracts. Both patients suffered from advanced cancer with metastases. One of the patients, who pre-operatively had severe pain in the right arm and chest, lived for two and a half months after the operation. During the last weeks there was some recurrence of the pain in the chest, but not in the arm. The other patient died from pulmonary metastases 14 days after the operation. She was relieved from the pain during the post-operative course.

In both cases some sensitivity was preserved on the contralateral side of the body, particularly on the trunk and face, in spite of complete destruction of the spinothalamic tract and medial lemniscus. It is suggested that transmission of sensory impulses through fibre systems other than the spinothalamic tracts and medial lemnisci in the brain-stem may be responsible for the preserved sensibility.

In the first case the tendon reflexes, extensor plantar response, and weak abdominal reflexes were increased, on the contralateral side of the lesion and probably also the tendon reflexes in the homolateral leg were somewhat exaggerated. Post-mortem examination of the brain-stem showed no involvement of the corticospinal fibres. The findings indicate that tendon reflexes as well as abdominal and plantar reflexes may be influenced by lesions of extrapyramidal fibre systems.

References

Berry, C. M., Anderson, F. D., and Brooks, D. C. (1956). *J. Neurophysiol.*, **19**, 144.

Bowsher, D. (1957). *Brain*, **80**, 606.

Bucher, V. M., and Bürgi, S. M. (1953). *J. comp. Neurol.*, **99**, 415.

Bucy, P. C. (1957). *Brain*, **80**, 376.

David, M., Talairach, J., and Hécaen, H. (1947). *Sem. Hôp. Paris*, **23**, 1651.

Dogliotti, A. M. (1938). *Anésth. et Analg.*, **17**, 143.

Foerster, O. (1936). In Bumke, O. and Foerster, O. *Handbuch der Neurologie*, Vol. **6**, p. 358. Springer, Berlin.

——, and Gagel, O. (1933). *Z. ges. Neurol. Psychiat.*, **144**, 313.

French, J. D., Verzeano, M., and Magoun, H. W. (1953). *A. M. A. Arch. Neurol. Psychiat.*, **69**, 505.

Fulton, J. F., and Keller, A. D. (1932). *The Sign of Babinski. A Study of the Evolution of Cortical Dominance in Primates.* Charles C. Thomas, Springfield, Illinois.

Glees, P., and Bailey, R. A. (1951). *Mschr. Psychiat. Neurol.*, **122**, 129.

Guiot, G., and Forjaz, S. (1947). *Rev. neurol.*, **79**, 733.

Häggqvist, G. (1936). *Z. mikr.-anat. Forsch.*, **39**, 1.

Hécaen, H., Talairach, J., David, M., and Dell, M. B. (1949). *Rev. neurol.*, **81**, 917.

Johnson, F. H. (1953). *Anat. Rec.*, **115**, 327.

—— (1954). *Ibid.*, **118**, 316.

Környey, St. (1936). In Bumke, O., and Foerster, O. *Handbuch der Neurologie*, Vol. **5**, p. 445. Springer, Berlin.

Lassek, A. M. (1954). *The Pyramidal Tract.* Charles C. Thomas, Springfield, Illinois. Amer. Lect. Ser. No. 233.

Leksell, L. (1957). In Olivecrona, H., and Tönnis, W. : *Handbuch der Neurochirugie*, Vol. **6**, p. 178. Springer, Berlin.

Melzack, R., Stotler, W. A., and Livingston, W. K. (1958). *J. Neurophysiol.*, **21**, 353.

Mettler, F. A. (1944). *J. comp. Neurol.*, **80**, 69.

——, and Zimmerman, F. T. (1943). *Ibid.*, **78**, 113.

Nathan, P. W., and Smith, M. C. (1955). *J. Neurol. Neurosurg. Psychiat.*, **18**, 250.

Nauta, W. J. H., and Kuypers, H. G. J. M. (1958). *In Reticular Formation of the Brain*, p. 3. [Henry Ford Hospital International Symposium]. Little, Brown and Co., Boston.

Papez, J. W. (1956). *Electroenceph. clin. Neurophysiol.*, **8**, 117.

Ramón y Cajal, S. (1909). *Histologie du Système Nerveux de l'Homme et des Vertébrés*, Vol. 1. Maloine, Paris.

Rasmussen, A. T., and Peyton, W. T. (1941). *Surgery*, **10**, 699.

——, —— (1948). *J. comp. Neurol.*, **88**, 411.

Riley, H. A. (1943). *An Atlas of the Basal Ganglia, Brain Stem and Spinal Cord.* Williams and Wilkins, Baltimore.

Rossi, G. F., and Brodal, A. (1957). *A.M.A. Arch. Neurol. Psychiat.*, **78**, 439.

Russell, G. V. (1954). *J. comp. Neurol.*, **101**, 237.

Scheibel, A. B. (1955). *Anat. Rec.*, **121**, 361.

Scheibel, M. E., and Scheibel, A. B. (1958). In *Reticular Formation of the Brain*, p. 31. Henry Ford Hospital, Detroit, Michigan.

Schwartz, H. G. (1950). *Surg. Clin. N. Amer.*, **30**, 1379.

Sjöquist, O. (1949). *IVe Congr. Neurol.*, **1**, 119.

Smyth, G. E. (1939). *Brain*, **62**, 41.

Torvik, A. (1957). *Amer. J. Anat.*, **100**, 1.

Tower, S. (1949). In Bucy, P. C. *The Precentral Motor Cortex*, 2nd ed., p. 149. University of Illinois Press, Urbana.

Walker, A. E. (1939). *J. comp. Neurol.*, **71**, 59.

—— (1940). *Arch. Neurol. Psychiat.* (*Chicago*), **43**, 284.

—— (1942a). *Arch. Surg.* (*Chicago*), **44**, 953.

—— (1942b). *Arch. Neurol. Psychiat.* (*Chicago*), **48**, 865.

—— (1950). *J. Lancet*, **70**, 279. Cited from White and Sweet (1955).

Walshe, F. M. R. (1947). *Brain*, **70**, 329.

White, J. C., and Sweet, W. H. (1955). *Pain, Its Mechanisms and Neurosurgical Control.* Charles C. Thomas, Springfield, Illinois.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 306

QUANTITATIVE ELECTROMYOGRAPHIC CHANGES ASSOCIATED WITH MUSCULAR WEAKNESS

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It has been shown that when a human muscle contracts the mean voltage of the electromyogram recorded from its surface increases with the force of the contraction (Bayer and Flechtenmacher, 1950; Inman, Ralston, Saunders, Feinstein, and Wright, 1952; Lippold, 1952). The relationship between tension and mean voltage is linear provided the contraction is isometric (Lippold, 1952). With an isotonic contraction the voltage depends also on the velocity of shortening of the muscle (Bigland and Lippold, 1954) so that the relationship only remains linear if that is held constant. If a muscle is fatigued by a prolonged isometric contraction the relationship between voltage and tension remains linear but is of a different slope. More electrical activity is associated with a given tension in the fatigued state (Edwards and Lippold, 1956). This is also true if the fatigue results from isotonic exercise (Scherrer, Samson, and Paléologue, 1954).

Under standardized conditions it is possible to record similar voltage/tension curves from the same subject on different occasions (Lenman, 1959). The experiments described here were carried out to determine the range of slope for the curves relating mean voltage and tension in the upper limb muscles of healthy subjects and of patients with weak muscles resulting from neurological or muscular disease.

Material and Methods

Simultaneous records were made of the isometric tension and the mean voltage recorded from surface electrodes over the biceps or triceps muscle of 12 healthy subjects and 26 patients with weakness of these muscles. The measurements were made by the method described before (Lenman, 1959). The tension was recorded by a strain gauge dynamometer in which the gauges formed part of a Wheatstone bridge fed by alternating current. The out-of-balance voltage, which was proportional to the applied force, was amplified and appeared on one channel of a pen recorder. The electromyogram was recorded from surface electrodes of 1 cm. diameter placed 3 cm. apart over the belly of the muscle. It was amplified and fed into an integrator circuit (Bates and Cooper, 1954) producing pulses of frequency proportional to the mean voltage. These appeared on the other channel of the pen recorder.

Curves relating tension (lb.) to mean voltage (mV) were made by recording these simultaneously while the subject carried out a series of isometric contractions at different tensions, the apparatus being calibrated as described before (Lenman, 1959). The ratio tension/electrical activity may be looked on as a measure of neuromuscular efficiency. In this presentation the reciprocal (voltage/tension) has been used so that the results can be compared with those of Lippold (1952).

Results

Experiments on Healthy Subjects.—The tension of the biceps or triceps was recorded simultaneously with the integrated electromyogram throughout a range of contractions in 12 healthy subjects. The mean values over five-second epochs were determined and voltage/tension curves constructed. The regression equation ($Y = a + bx$) for each curve was calculated and the slope (b) was expressed as a regression coefficient (Fig. 1).

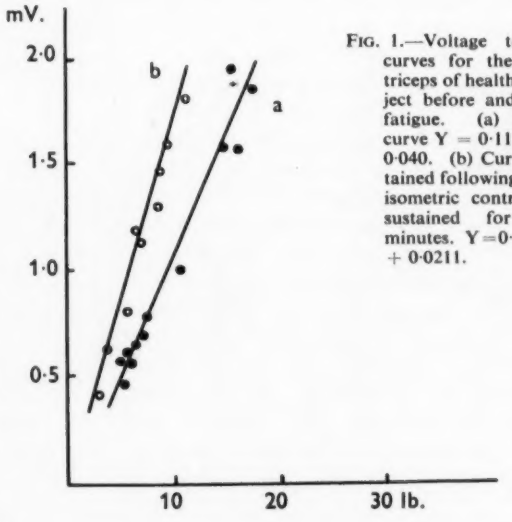

FIG. 1.—Voltage tension curves for the right triceps of healthy subject before and after fatigue. (a) Initial curve $Y = 0{\cdot}1110X - 0{\cdot}040$. (b) Curve obtained following weak isometric contraction sustained for five minutes. $Y = 0{\cdot}1675X + 0{\cdot}0211$.

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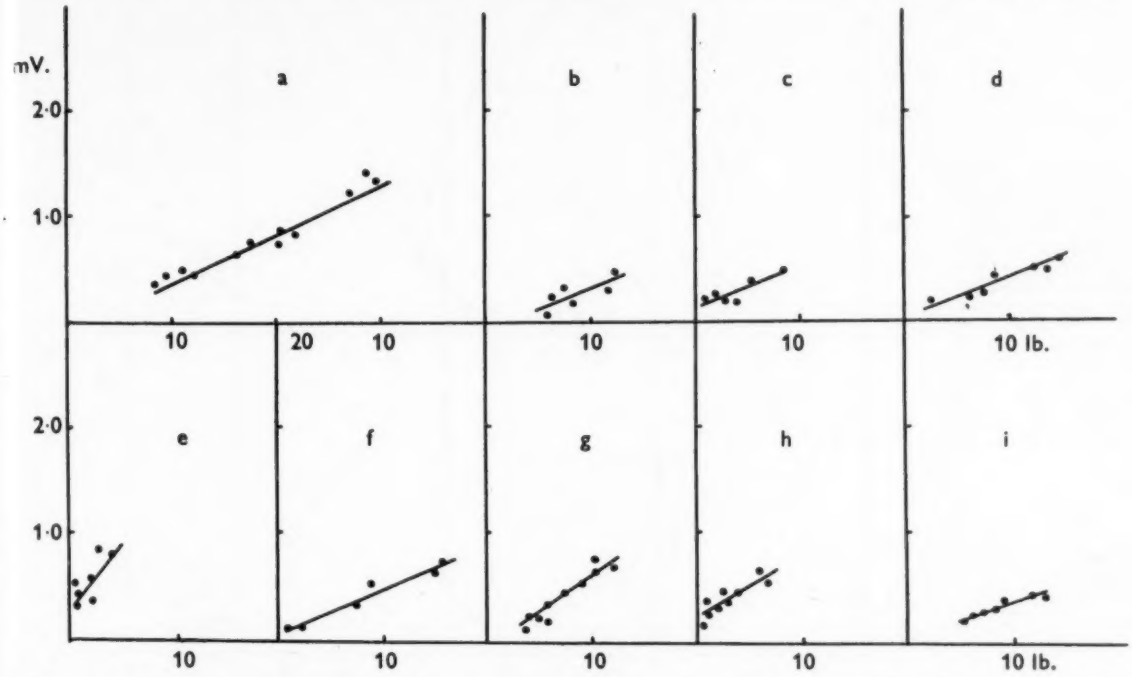

FIG. 2.—Voltage tension curves from biceps of healthy subject and eight patients with neurogenic weakness. (a) Healthy subject b = 0·0521; (b) Case 1, zoster myelitis, b = 0·0358; (c) Case 2, pseudobulbar palsy, b = 0·0388; (d) Case 3, neuralgic amyotrophy, b = 0·0427; (e) Case 4, syringomyelia, b = 0·1077; (f) Case 5, polyneuritis, b = 0·0442; (g) Case 6, b = 0·0543; (h) Case 7, b = 0·0571; (i) Case 8, b = 0·2714; (g), (h), and (i) all motor neurone disease.

Curves obtained from 12 biceps muscles of 10 subjects had a slope which ranged from 0·0290 to 0·0875 with a mean regression coefficient of 0·0484 and a standard deviation of 0·0169. With six triceps muscles of six subjects the slope was steeper, ranging from 0·0470 to 0·1553, with a mean of 0·0972 and a standard deviation of 0·0428.

Fig. 1 shows the effect of a prolonged fatiguing isometric contraction on the slope of the curve for one of these triceps muscles. The increased slope indicates decreased neuromuscular efficiency as defined above.

Patients with Disease of the Nervous System.—These patients had muscular weakness resulting from disease of the nervous system, such as motor neurone disease, peripheral neuritis, or cerebral vascular disease. The slopes of the voltage/tension curves fell within the normal range. The high voltages associated with maximal contractions of normal muscles were not obtained because with these patients the maximal contractions were very much weaker. Over the range of tensions they were able to exert, the voltages registered were of the same order of magnitude as those of the healthy subjects. The slope of the curves for eight biceps muscles of eight subjects in this group (Fig. 2) ranged from 0·0271 to 0·1077 with a mean of 0·0510 and a standard deviation of 0·0334. The difference between this mean and that for the 10 normal biceps muscles was not significant. The slope of the voltage/tension curve for the triceps of Case 22 (motor neurone disease) was within the normal range (Fig. 5).

Patients with Primary Muscular Disease.—Similar experiments were carried out on patients with weak muscles as a result either of a muscular dystrophy or polymyositis. Voltage/tension curves were constructed for two triceps muscles of two patients with muscular dystrophy and six biceps muscles of four patients with muscular dystrophy and two with polymyositis. The curves were of steeper slope than in the previous groups (Fig. 3) indicating decreased neuromuscular efficiency.

The regression coefficients for the triceps muscles were 0·9798 (Fig. 5) and 0·4291. For the six biceps they ranged from 0·0723 to 0·2575 (Fig. 3) with a mean of 0·1427 and a standard deviation of 0·0694. The significance of t for the difference between the mean slope of the curves of these six muscles and of those of the 12 healthy biceps was 0·001.

Patients with Poliomyelitis.—Nine patients who had weak muscles as a result of poliomyelitis at least one year previously were studied. The voltage/tension curves recorded were of particularly steep slope. The regression coefficients for the seven

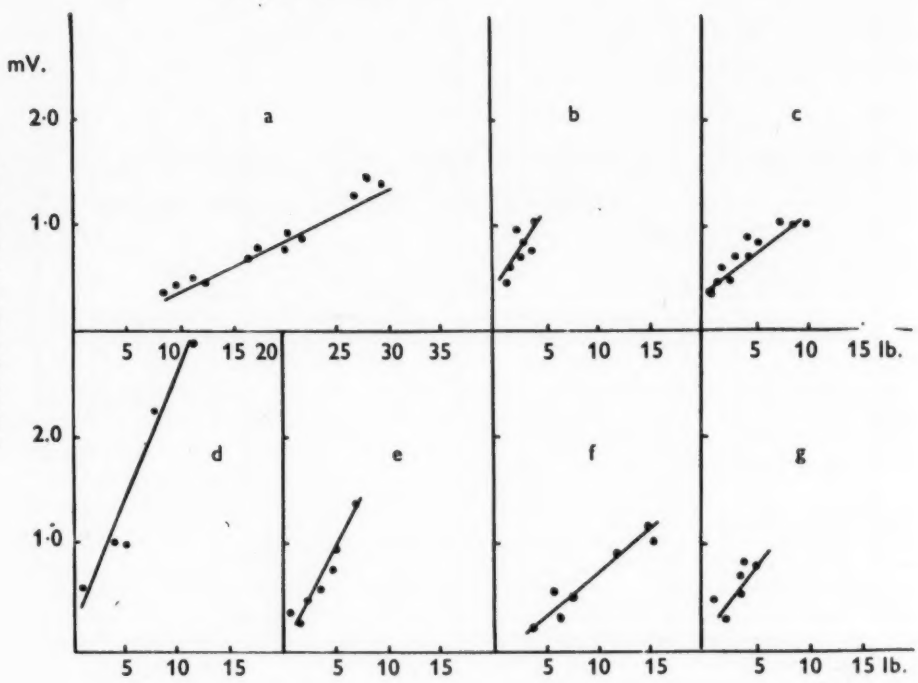

FIG. 3.—Voltage tension curves from biceps of a healthy subject and six patients with primary muscular disease (Cases 11 and 12 polymyositis, the rest muscular dystrophy). (a) Healthy subject, b = 0·0521; (b) Case 9, b = 0·1629; (c) Case 10, b = 0·0754; (d) Case 11, b = 0·2575; (e) Case 12, b = 0·1667; (f) Case 13, b = 0·0723; (g) Case 14, b = 0·1216.

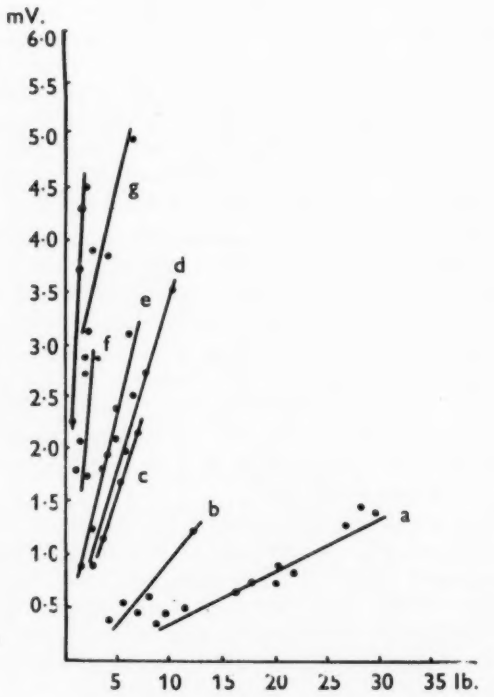

FIG. 4.—Voltage tension curves from biceps of a healthy subject and seven patients with weakness as a result of poliomyelitis. (a) Healthy subject, b = 0·0521; (b) Case 15, b = 0·1302; (c) Case 16, b = 0·4430; (d) Case 17, b = 0·3320; (e) Case 18, b = 0·4033; (f) Case 19, b = 1·0350; (g) Case 20, b = 0·4334; (h) Case 21, b = 1·7611.

biceps studied ranged from 0·1302 to 1·7611 with a mean of 0·6842 and a standard deviation of 0·5634 (Fig. 4). The significance of t for the difference between this mean and that of the 12 normal biceps was 0·001. The slope of the curve for the triceps of Case 24 was 0·3809 (Fig. 5) and of Case 25 was 0·2997.

The values of mean voltages associated with maximal contractions were higher in this group than in the other groups although the tensions produced were low. Thus Case 24 registered a mean voltage of 6·0 mV. during a maximal contraction of 15 lb. tension. The highest mean voltage recorded from a healthy muscle in this study was about 3·0 mV. (tension over 30 lb.).

Discussion

Bigland and Lippold (1954) in their study of the relationship between force, velocity, and integrated electrical activity in human muscles concluded that these three factors are interdependent and that the integrated electrical activity provides a measure of the number of active fibres and their frequency of activation. This is supported by the subsequent observation that in fatigued muscle the relationship between tension and integrated electrical activity is still linear but is of different slope. In a fatigued muscle more electrical activity is associated with a given tension (Edwards and Lippold, 1956). This tension is maintained by recruitment of more

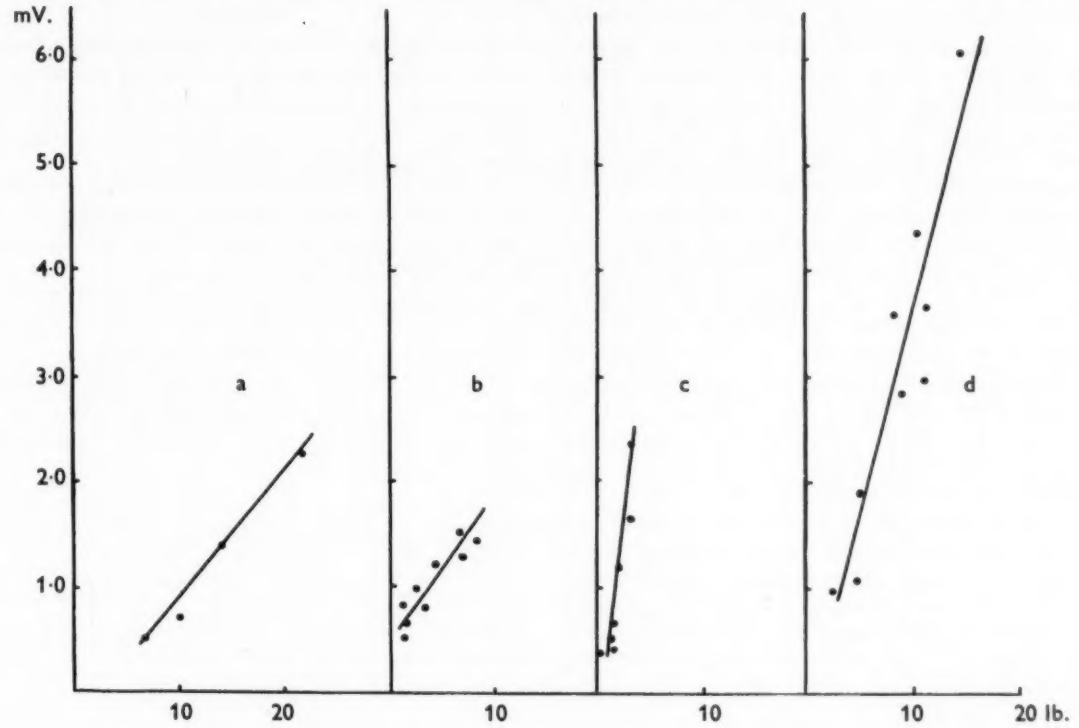

FIG. 5.—Voltage tension curves from triceps of a healthy subject and three patients with muscular weakness. (a) Healthy subject, b = 0·1386; (b) Case 22, motor neurone disease, b = 0·1292; (c) Case 23, muscular dystrophy, b = 0·9798; (d) Case 24, poliomyelitis, b = 0·3809.

fibres. The slope of the curve relating voltage to tension may thus be regarded as a measure of the efficiency of the individual fibres composing a muscle (in fact the reciprocal of efficiency). The more effective the fibres as contractile units, the fewer will be required to maintain a given tension and the less steep will be the voltage/tension curve. For weak muscle the following relationship could be predicted.

If a muscle becomes weak through interference with its nerve or from an upper motor neurone lesion so that the full number of motor units can no longer be activated one would expect no alteration in the relationship between voltage and tension. The voltage and tension associated with a maximal contraction would be less in proportion to the reduction in the number of available motor units. Where weakness is due to a structural change in the muscle fibres, so that these can no longer exert their full tension, the position would be analogous to that obtaining in a fatigued muscle. To maintain a given tension, a larger number of fibres would be activated, the integrated voltage would be greater and the slope of the voltage/tension curve would be steeper.

The first group of patients reported here had muscular weakness resulting from disease of the nervous system affecting either the spinal cord or the peripheral nerves. The slopes of the voltage/tension curves obtained from these patients lay within the normal range. This accords with the view that the loss of strength in these patients is due to a reduction in the number of available motor units.

The second group of patients had weakness resulting from disease of the muscles. Six of the eight cases had voltage/tension curves which were strikingly steeper than normal. The remaining two cases had curves with regression coefficients within the normal range though considerably greater than the mean normal value. This alteration in slope indicates that the contractile force of the muscle fibres was reduced without a corresponding reduction in the size of their action potentials (lowered mechanical efficiency). It is possible that the voltage/tension curve may be of diagnostic value in primary muscular disorders and may also be of interest in studying the progress of the disease.

The nine patients who had weakness resulting from poliomyelitis all had curves considerably steeper than the normal and unexpectedly high voltages were associated with maximal contractions although the relationship between voltage and

tension was still linear. All of these patients differed from the first group with disease of the nervous system in that a long period—sometimes several years—had elapsed since the disease was active. Animal experiments have demonstrated that in partially denervated muscle recovery proceeds by the surviving nerve fibres sprouting to supply denervated muscle fibres, so that the animal ends with a reduction in the number of motor units which are of greater size (Van Harreveld, 1945; Hoffman, 1950). Coërs (1954) and Wohlfart (1955) have described the same process in human muscle during recovery from poliomyelitis. If the muscles of patients in the recovering stages of poliomyelitis are examined with concentric needle electrodes it is found that the mean amplitude and the mean duration of the action potentials are greater than normal (Hertz, Madsen, and Buchthal, 1954). It is reasonable to regard these large action potentials as originating from motor units enlarged by collateral sprouting. The high mean voltages recorded here may be the result of this increase in size of the motor units. The increase in slope of the voltage/tension curves seems to suggest that motor units enlarged by collateral sprouting are less efficient contractile units, fibre for fibre, than units of physiological size.

Collateral sprouting is not a phenomenon confined to recovering poliomyelitis but is also known to occur in other conditions, notably motor neurone disease (Coërs, 1954; Wohlfart, 1957). In this condition large motor units are frequently observed on routine electromyography with needle electrodes. It is of interest therefore that the few cases of motor neurone disease studied here showed voltage/tension curves within the normal range of slope. The disease is usually rapidly progressive and it is likely that in these patients the rate of destruction of anterior horn cells was proceeding sufficiently fast to outstrip any process of recovery.

Summary

The range of slope of the curves relating integrated mean voltage to isometric tension of the upper arm muscles has been determined for a group of healthy subjects. Curves for the triceps are steeper than those obtained from the biceps.

In patients with muscular weakness due to disease of the nervous system reducing the number of available motor units the slope of the voltage/tension curves lies within the normal range.

In neuromuscular fatigue, myopathic muscle, and late cases of poliomyelitis the slope is increased, indicating reduced mechanical efficiency.

These results are as predicted from theoretical considerations except in poliomyelitis. It is suggested that this discrepancy is due to collateral sprouting of surviving neurones.

I wish to thank those physicians and surgeons in the Edinburgh hospitals who allowed their patients to be studied. Dr. J. A. Simpson provided facilities for this study and his interest, encouragement, and helpful criticism are greatly appreciated. The work was supported by a grant from the Scottish Hospitals Endowments Research Trust which is gratefully acknowledged.

References

Bates, J. A. V., and Cooper, J. D. (1954). *J. Physiol.* (*Lond.*), **123**, 28P.

Bayer, H., and Flechtenmacher, C. (1950). *Arbeitsphysiologie*, **14**, 261.

Bigland, B., and Lippold, O. C. J. (1954). *J. Physiol.* (*Lond.*), **123**, 214.

Coërs, C. (1954). *Les Variations Structurelles Normales et Pathologiques de la Jonction Neuromusculaire.* Les Editions *Acta Medica Belgica*, Bruxelles, pp. 81-105.

Edwards, R. G., and Lippold, O. C. J. (1956). *J. Physiol.* (*Lond.*), **132**, 677.

Hertz, H., Madsen, A., and Buchthal, F. (1954). *J. Bone Jt Surg.*, **36-A**, 902.

Hoffman, H. (1950). *Aust. J. exp. Biol. med. Sci.*, **28**, 383.

Inman, V. T., Ralston, H. J., Saunders, J. B. de C. M., Feinstein, B., and Wright, E. W. jr. (1952). *Electroenceph. clin. Neurophysiol.*, **4**, 187.

Lenman, J. A. R. (1959). *J. Neurol. Neurosurg. Psychiat.*, **22**, 182.

Lippold, O. C. J. (1952). *J. Physiol.* (*Lond.*), **117**, 492.

Scherrer, J., Samson, M., and Paléologue, A. (1954). *J. Physiol. Path. gén.*, **46**, 887.

Van Harreveld, A. (1945). *Amer. J. Physiol.*, **144**, 477.

Wohlfart, G. (1955). *Nord. Med.*, **54**, 1075 (English summary p. 1080).

—— (1957). *Neurology*, **7**, 124.

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THE DIAPHRAGM IN DYSTROPHIA MYOTONICA

BY

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In a previous publication, Caughey and Gray (1954) reported three patients out of 25 with dystrophia myotonica in whom the diaphragm was raised on one side. Rouques (1931) in his case records described another case but makes no comment on it. Caughey and Gray suggested that this incidence (12%) of diaphragmatic lesions may be statistically significant and may come to be recognized as one of the variable features of the disease. Since the original report, Benaim and Worster-Drought (1954) have reported a case of dystrophia myotonica affecting both halves of the diaphragm, causing pulmonary hypoventilation with anoxaemia and secondary polycythaemia, and Bashour, Winchell, and Reddington (1955) have reported a case of dystrophia myotonica with cyanosis, polycythaemia, and unilateral elevation of the diaphragm. Recently we have had an opportunity to study two further cases of dystrophia myotonica with an elevated diaphragm, and, in one of them, to obtain a biopsy of the diaphragm. It is considered that this report is justified in view of new points which it raises.

Case Reports

Case 1.—A man, aged 62 years, a civil servant, was admitted to the Postgraduate Hospital, Hammersmith, London, under the care of Dr. Milne, who kindly referred him to me. He was well until 1953 when he began to lose weight. He was investigated at the Paddington Chest Clinic, but no abnormality of the chest was discovered and the E.S.R. was not raised.

In November, 1953, he developed an attack of right upper abdominal colic which persisted for several hours. After that attack he had a series of attacks similar in nature but varying in severity. With each he developed flatulence and anorexia and in one attack his urine became dark and he became jaundiced.

To direct questioning he stated that his neck had been weak for several years; his vision had deteriorated lately. He had not noticed any difficulty in relaxing his grip. His mother was alive and well. His father died of a stroke and one sister had had a stroke. He had had no children and his libido had failed somewhat, and apareunia had existed for four years.

On examination he was moderately well developed and well nourished. He was slightly jaundiced. The ocular fundi were normal and there were bilateral lens opacities. He had a myopathic facies with slight ptosis. There was no mechanical myotonia of the tongue. The sternomastoid muscles were almost completely wasted and the other anterior cervical muscles were wasted and weak. The upper extremities were moderately well developed. There was no wasting or weakness. There was no active or mechanical myotonia. Sensory appreciation was normal; the deep reflexes were present and equal; the abdominal muscles were not weak. There was no wasting of the lower extremities. The tone, power, and coordination were normal. There was no mechanical myotonia of the small muscles of the feet. The deep reflexes were present and equal. There was tenderness over the gall bladder region. The serum bilirubin level was 6·9 mg./100 ml.; the alkaline phosphatase 27·7 units; the van den Bergh test gave a positive direct reaction. The albumin-globulin ratio and the total protein content were normal. The prothrombin time was 30 to 45 seconds.

Radiography of the skull was normal. The chest film (Fig. 1) showed elevation of the ventral part of the right half of the diaphragm and this was confirmed by the lateral film. Paradoxical movement was seen on screening. A cholecystogram revealed stones and impaired gall bladder function.

Operation.—Professor I. Aird on May 4, 1954, performed a cholecystectomy and took biopsies from the right half of the diaphragm, the sternomastoid, and rectus muscles. Dr. Harrison reported as follows on the muscle biopsies:

> Section of the rectus abdominis, diaphragm, and the sternomastoid muscles show changes which vary in degree from fairly minimal changes in the rectus to more marked disease of the diaphragm and sternomastoids. There is an abnormal variation in the size of the muscle fibres from 120 microns to grossly atrophied fibres seen in a few foci in the diaphragm, which are only a few microns across. There are areas of fibrosis in relation to atrophic fibres which may be interpreted as condensation of perimysin. There is an excess of adipose tissue, more particularly in the sternomastoid muscle where fibres are uniformly small. Occasional fibres show migration of nuclei from their usual peripheral situation to become aligned in the centre of the fibre, but this is not an outstanding feature. There is no cellular reaction or infiltration.

Case 2.—Mr. J.B.W., aged 50 years, was first admitted to the North Canterbury Hospital in 1950 for investigation of increasing muscular weakness. The first symptom noticed by the patient was that when he tried to turn a key his right hand cramped. At the time of admission to hospital there was weakness of the legs which had been present for 10 years and difficulty in gripping objects which had been noticed for six years. The patient has not been able to support his head and could not get up from the lying position. There was also loss of libido and the patient volunteered that his voice had become "thick".

On examination he was an obese man with an expressionless face, ptosis of the eyelids, and facial weakness. Speech was slurred. There was frontal baldness but the facial hair was normal and body hair grew profusely.

The testicles were small and atrophic. Cataracts were not seen.

The apex beat of the heart was 3 in. from the midline. The heart sounds were regular but of poor quality. The pulse was 70 and blood pressure was 140/70 mm. mercury. The percussion note over the chest was not impaired but a few scattered rales were heard.

There was marked weakness of the facial muscles, ptosis of the eyelids, and wasting and weakness of the sternomastoid muscles. There was wasting and weakness of the forearms and of the small muscles of the hands. The legs were also wasted and weak and there was bilateral dropfoot. There was voluntary and percussion myotonia of the hands. The deep reflexes were all absent and the plantar responses were flexor in type and the abdominal reflexes were brisk. No other abnormality was found in the central nervous system.

Special Investigation.—A lumbar puncture showed a clear fluid and the pressure was 150 mm. of water. The Queckenstedt test was normal; the Pandy reaction was 1+ and the protein 60 mg. per 100 ml. The Wassermann reaction was negative. The patient was treated with vitamin E and discharged home. Two years later diabetes was diagnosed. The patient was again in hospital four years after the original admission on account of uncontrolled diabetes mellitus. At that time his physical condition deteriorated. Radiographs of the chest revealed localized elevation of the anterior portion of the right diaphragm and a radiograph of the skull showed generalized thickness of the calvarium, large sinuses, and a small pituitary fossa. The fasting blood sugar was 333 mg. per 100 ml. and there was a lenticular opacity on the right. From that time the patient's condition deteriorated steadily and he died at the age of 56 years. There was no necropsy.

The cases previously reported are summarized in Table I together with the present cases.

Discussion

We have found few references to involvement of the diaphragm in the same pathological process as the skeletal muscles in patients with dystrophia myotonica. Sekiya (1940) points out that in a case of myopathy the diaphragm is involved late.

TABLE I
CLINICAL FINDINGS

Case and Author	Sex and Age (yr.)	Family History	Cataract	Myotonia			Wasting			Skull			Diaphragm
				Mechanical	Active	Face	Sterno-mastoid	Arm	Leg	Pituitary Fossa	Calvarium	Hyperostosis	
1. G.L. Caughey and Gray	M 50	Negative	Posterior polar	Hands and tongue	Grip +++	+	+	+	+	Small	Thick	No	R. side elevated. Very slight respiratory excursion
2. E.W. Caughey and Gray	F 40	Positive	Bilateral	Tongue and hands	Grip +++	++	++	++	++	Very small	+++	++	Left side elevated, immobile
3. E.H. Caughey and Gray	F 55	?	Bilateral cataracts	Nil	Nil	+	+++	+++	—	Small to normal	+++	++	Right side elevated; excursion, R. 1 cm., L. 4 cm.
4. Rouques Case	M 38	Positive	Bilateral cataracts	Yes	Grip	+	+++	+	+	Small	—	++	Left side inner half. Costophrenic angle is obliterated on the left
5. S.G. Benaim and Worster-Drought	M 38	Parents had cataracts	Bilateral polar cataracts	Hands and tongue	+++	Nil	+++	+++	++	Normal	Normal	Normal	Bilateral elevation of diaphragm
6. F. Bashour	M 57	Father 1 brother 1 sister	Bilateral cataracts	Not recorded	Not recorded	+	+++	++	++	—	—	—	Elevation right leaf of diaphragm with restricted movement of the entire diaphragm
7. M.C. Present case	M 62	Nil	Bilateral cataracts	Nil	Nil	+	+++	—	—	Normal	Normal	Normal	Elevation of ventral portion of R. diaphragm. Paradoxical movement of the diaphragm
8. J.B.W. Present case	M 50	Father had myotonia	R. eye	Yes	Yes	+	++	+	+	Small	Thick	—	Elevation sternal portion of right diaphragm

Robinson, Mosberg, and Lowe (1950) made a study of diaphragmatic movements in various neurological disorders and investigated a group of six patients with unspecified muscular disorders where there was marked wasting of the shoulder girdle muscles but no change in the diaphragmatic movement. Benaim and Worster-Drought (1954) were able to demonstrate electromyographically myotonia of the intercostal muscles, but were unable to take electromyograms from the diaphragm. The severity of myotonia was such as to interfere with respiration and caused severe anoxia due to hypoventilation. Bashour *et al.* (1955), reporting on a case of dystrophia myotonica, described right-sided elevation of the diaphragm, also cyanosis, polycythaemia, greatly decreased vital capacity, and increased pressure in the pulmonary artery (38 mm.), and presumed that decreased movement of the respiratory muscles was the cause of the hypoventilation.

In the initial publication Caughey and Gray (1954) reported unilateral elevation of the diaphragm in three cases. Subsequently Benaim and Worster-Drought (1954) reported a case with both halves of the diaphragm affected. The two cases reported here are of interest on account of the partial elevation of one half of the diaphragm. It appears to be the sternal portion of the right diaphragm which is involved in both cases. Thus it appears that in dystrophia myotonica we may have involvement of both halves of the diaphragm, half the diaphragm, or a portion only of one half.

In a previous publication one of us (J.E.C.) was unable to observe under the *x*-ray screen delayed relaxation of the diaphragm to command. In the first of the two cases reported here, we were able to obtain biopsies of the various muscles, including the diaphragm. The sternomastoid muscle was severely involved in the atrophic process and the diaphragmatic muscle showed localized, but definite changes such as variation in the size of the muscle fibres, increase of connective and fatty tissue, and formation of central chains of nuclei. This report presents definite evidence that the diaphragm also might be involved in the same dystrophic process as other skeletal muscles but probably late in the disease process.

Black and Ravin (1947), in their report on the necropsies of five cases of dystrophia myotonica, were unable to find definite abnormal changes in the diaphragm. In the differential diagnosis, lesions of the spinal cord or phrenic nerve could be excluded. Eventration is a congenital lesion and always occurs on the left side, and in cases of left-sided elevation of the diaphragm should be seriously considered, as it might be one of the congenital abnormalities present in a case of dystrophia myotonica.

As previously suggested we are of the opinion that elevation of the diaphragm should come to be accepted as one of the variable features of dystrophia myotonica.

Summary

Two cases of dystrophia myotonica with right-sided elevation of the diaphragm are reported.

In one case biopsy of the diaphragmatic muscle showed definite histological changes of a muscle dystrophy.

Elevation of the diaphragm may be partial, unilateral, or bilateral, and should come to be accepted as a variable feature of dystrophia myotonica.

We are grateful to Dr. Milne, of the Postgraduate Hospital, Hammersmith, who referred Case 1, and to Dr. Cunningham, of the North Canterbury Hospital, who gave us access to the second case. We are grateful for secretarial assistance from Mrs. G. Sim and Mrs. J. Pilkington.

References

Bashour, F., Winchell, P., and Reddington, J. (1955). *New Engl. J. Med.*, **252**, 768.

Benaim, S., and Worster-Drought, C. (1954). *Med. Ill.*, **8**, 221.

Black, W. C., and Ravin, A. (1947). *Arch. Path. (Chicago)*, **44**, 176.

Caughey, J. E., and Gray, W. G. (1954). *Thorax*, **9**, 67.

Robinson, P. K., Mosberg, W. H., and Lowe, R. C. W. (1950). *J. Neurol. Neurosurg., Psychiat.*, **13**, 296.

Rouques, L. (1931). *La Myotonie Atrophique*, p. 40. Legrand, Paris.

Sekiya, M. (1940). *Orient. J. Dis. Infants*, **28**, 8.

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MYOPATHY IN CUSHING'S SYNDROME

BY

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Muscular weakness is a well-known feature of Cushing's syndrome and was mentioned by Cushing (1932a and b) in his original description of the disease. It has been suggested that the muscular weakness and the atrophy sometimes occurring may be due to increased breakdown of proteins (Soffer, 1951) or to decreased protein synthesis (Lukens, 1954).

So far as we are aware, no systematic investigation of the occurrence and extent of the paresis in Cushing's syndrome has been reported in the literature. Neither do morphological alterations in the muscle appear to have been studied. Marburg (1933) reported a case of Cushing's syndrome with weakness of the pelvic girdle musculature in which necropsy revealed histological changes of the muscular dystrophy type. He pointed out, however, that in this case there was a combination of Cushing's syndrome and progressive muscular dystrophy. Accordingly, the pathological process underlying the muscular weakness in Cushing's syndrome is unknown.

We have studied the motor function in six patients with typical Cushing's syndrome clinically and electromyographically. Muscle biopsy was done in four of them.

Five of the patients had weakness involving primarily the proximal muscles of the lower limbs, and in them the electromyographic examination revealed signs of myopathy. The histological studies disclosed degeneration of muscle fibres.

Case Reports

Case 1.—A woman, born in 1916, developed the classical features of Cushing's syndrome in 1950. Since 1957 she had had weakness of the legs, had difficulty in climbing stairs, and was unable to mount a ladder. She had also noticed some difficulty in raising her arms over the head. She had not received any treatment.

Neurological Examination (*October*, 1958).—There was moderate weakness of dorsiflexion of the feet and toes and considerable weakness of extension at the knees and of flexion, extension, and adduction at the hips. Trendelenburg's test was positive bilaterally. She was unable to step up on to a chair or to rise from the squatting position without the aid of her hands. She was unable to walk on her heels. There was slight weakness of forward flexion and abduction at the shoulders. There was no definite atrophy. The muscle reflexes were normal. The plantar responses were flexor. Sensation was unimpaired.

Electromyographic Examination.—Examination of the quadriceps and anterior tibial and deltoid muscles revealed signs of myopathy, most pronounced in the quadriceps.

Histological Report.—Transverse sections of the right quadriceps muscle showed slight infiltration of fat cells between the muscle bundles. The connective tissue was moderately increased and in one place dense and hyaline. The endomysial connective tissue was also slightly increased in places. Most of the muscle fibres were somewhat thin, but as a rule the polygonal contour was retained. At the edge of one muscle bundle was seen a group of rounded fibres which were hyalinized and somewhat larger than the other fibres. The striation was preserved in most areas. Most of the sarcolemmal nuclei had retained their shape and hypolemmal position; some nuclei were small, dark, and elongated and relatively increased in number. Occasional lymphocytes were present in the interstitial tissue. The blood vessels and nerves were normal.

Case 2.—A man, born in 1939, in whom a typical Cushing syndrome developed in 1953. Since 1956 he had noticed slight weakness of the legs. Bilateral adrenalectomy was performed in two stages in August and September of 1958. The right adrenal showed a moderate cortical hypertrophy, the left adrenal was normal. After the operation he had received 50 mg. of cortisone daily.

Neurological Examination (*October*, 1958).—There was slight weakness of extension at the left knee and of all movements at the hips. Trendelenburg's test was negative. There was no weakness of the arms. There was no evidence of muscular atrophy. The muscle reflexes were normal. The plantar responses were flexor. Sensation was unimpaired.

Electromyographic Examination.—Examination of the quadriceps and anterior tibial muscles revealed signs of myopathy, most pronounced in the quadriceps.

Case 3.—A woman, born in 1925, developed Cushing's syndrome in 1950, rapidly increasing in severity. The

disease was accompanied by progressive weakness of the legs. She had difficulty in walking and frequently fell down. At the end of 1953 a right subtotal adrenalectomy was performed and a cortical adenoma the size of a large pea was resected. After the operation she had received 50 mg. of cortisone daily. During the following year the physical abnormalities practically disappeared, but an extremely severe pigmentation appeared over the entire body and on the mucous membranes. Power in the legs was slightly increased.

Neurological Examination (*October*, 1958).—There was moderate weakness of extension at the knees and of flexion and adduction at the hips. She was unable to step up onto a chair with the left foot and only with difficulty with the right foot without the aid of her hands. She could only just rise from the squatting position. Trendelenburg's test was negative. There was no weakness of the arms. There was no evidence of muscular atrophy. The muscle reflexes were normal. The plantar responses were flexor. Sensation was unimpaired.

Electromyographic Examination.—Examination of the quadriceps, anterior tibial, deltoid, and first dorsal interosseous muscles revealed signs of myopathy, most pronounced in the quadriceps.

Histological Report.—Most of the muscle bundles of the right quadriceps had normal configuration. They were separated by slightly increased amounts of connective tissue and fat. A number of degenerated fibres were seen lying in groups but also singly among normal muscle fibres. Some of them were comparatively large. A few fibres were completely hyalinized. The sarcolemmal nuclei had for the most part retained their normal shape and hypolemmal position; some were small, dark, and arranged in longitudinal rows and relatively increased in number. There were no inflammatory cells. The blood vessels and nerves were normal.

Case 4.—A woman, born in 1918, since 1954 had presented the signs and symptoms of Cushing's syndrome, including weakness of the legs, most pronounced when climbing stairs. Earlier her muscles had been strong and she had taken part in athletic sports. In May, 1958, a basophilic hypophyseal adenoma was extirpated after which the Cushing symptoms largely disappeared. After the operation she received 25 mg. of cortisone daily. The weakness of the legs, however, persisted.

Neurological Examination (*October*, 1958).—There was moderate weakness of extension at the knees and slight weakness of all movements at the hips, particularly of flexion, abduction, and adduction. She had great difficulty in stepping up onto a chair and rising from the squatting position without the aid of her hands. Trendelenburg's test was negative. There was no weakness of the arms. There was no evidence of muscular atrophy. The muscle reflexes were normal. The plantar responses were flexor. Sensation was unimpaired.

Electromyographic Examination.—Examination of the quadriceps muscles revealed signs of myopathy.

Histological Report.—In some areas of the right quadriceps the muscle fibres were replaced by dense hyaline connective tissue and to a lesser degree by fat. In places the endomysial connective tissue was also slightly thickened. The diameter of the fibres varied: many were normal, others thin or slightly hypertrophic. In cross sections the fibres usually appeared rounded. In most of the fibres striation was intact. Most of the sarcolemmal nuclei had retained their normal shape and position: some, especially in the thin fibres, were small, dark, and occasionally arranged in longitudinal rows; some had migrated centrally. Isolated fibres were hyalinized and contained dark, shrunken nuclei which sometimes lay in clumps. In places single or rows of pyknotic sarcolemmal nuclei lay free in the connective tissue or close to thin degenerated fibres. In one area there was a suggestion of regeneration. There were no inflammatory cells. The blood vessels and nerves were normal.

Case 5.—A woman, born in 1906, developed the classical features of Cushing's syndrome in the late thirties and they steadily progressed. In 1945, she received a course of *x*-ray irradiation to the pituitary with temporary improvement. In 1950, she was given a second course of *x*-ray irradiation and was placed on testosterone propionate. During the next two years the symptoms regressed but since 1952 her condition had remained comparatively stationary with mild, but distinct signs of the Cushing syndrome. Since 1948 she had noticed weakness of the legs and difficulty in climbing stairs. There was also slight loss of power in the arms, manifested chiefly by difficulty in lifting heavy objects.

Neurological Examination (*October*, 1958).—There was slight weakness of dorsiflexion of the feet and toes and moderate weakness of extension at the knees and of flexion at the hips. She was unable to mount a chair or rise from the squatting posture without the aid of her hands. Trendelenburg's test was negative. There was slight weakness of forward flexion and abduction at the shoulders. There was no muscular atrophy. The right quadriceps reflex was weaker than the left. All other muscle reflexes were normal and bilaterally equal. The plantar responses were flexor. Sensation was unimpaired.

Electromyographic Examination.—Examination of the quadriceps, anterior tibial, and deltoid muscles revealed signs of myopathy, most pronounced in the quadriceps.

Histological Report.—In places in the left quadriceps the muscle fibres were replaced by fat and, to a lesser degree, by connective tissue. Most of the fibres were slightly thinner than normal but had retained their polygonal shape and striation. A few fibres, however, were hyalinized and striation obscured. Many of the sarcolemmal nuclei were small, dark, and elongated. In the thin fibres the nuclei were relatively increased and sometimes arranged in longitudinal rows; a few were centrally placed. The interstitial tissue contained a few lymphocytes. The blood vessels and nerves were normal.

Case 6.—A woman, born in 1912, since 1953 had presented the clinical features of Cushing's syndrome. In February, 1955, the right suprarenal gland was removed and was found to contain a zona reticularis tumour the size of a walnut. After the operation all signs and symptoms of Cushing's syndrome disappeared. She had never noticed any weakness of the limbs.

Neurological Examination (*October*, 1958).—There was no evidence of muscular weakness or wasting. The muscle reflexes were normal. The plantar responses were flexor. Sensation was normal.

Electromyograms from the quadriceps muscles were normal.

Results

Muscular Signs and Symptoms.—Five patients had weakness of the muscles of the pelvic girdle and thighs. In two of them (Cases 3 and 4) this was one of the first symptoms of the disease and in both had progressed rapidly. In three patients (Cases 1, 2, and 5) the muscular weakness began three, seven, and 10 years, respectively, after the onset of the disease, when the other symptoms were severe, and had developed slowly, becoming marked in two of them. Case 6 had no muscular weakness.

Case 1 had a slight waddling gait and a positive Trendelenburg's test bilaterally. The remaining patients had a normal gait. Four patients (Cases 1, 3, 4, and 5) were unable to step up onto a chair or rise from the squatting position without the aid of their hands.

Two patients (Cases 1 and 5) also had weakness of the muscles of the shoulder girdle and of dorsiflexion of the feet. In both, this had developed later and was less pronounced than the weakness in the lower limbs. The abdominal, neck, or facial muscles were not involved.

None of the patients had muscular pain or tenderness. There was no definite atrophy and no evidence of pseudohypertrophy. Muscular fasciculations were not observed.

One patient (Case 5) had unilateral impairment of the quadriceps reflex. The muscle reflexes were otherwise normal. The plantar responses were always flexor. There were no sensory changes.

In three patients (Cases 3, 4, and 5) treatment had resulted in partial or complete regression of the Cushing syndrome. The muscular weakness, however, persisted, although in Case 3 there was a slight improvement of muscle power.

Electromyography.—None of the electromyograms showed spontaneous fibrillation potentials or positive sharp waves. The insertion activity was normal. There were no signs of increased muscular irritability or denervation.

During maximal voluntary contraction a large number of action potentials were recorded, producing the normal interference pattern. Accordingly, there was no gross reduction in the number of motor units.

The appearance of the individual potentials, however, was altered in five patients. This abnormality consisted of a general reduction in the size and duration of the individual potentials and an increased proportion of polyphasic potentials. The changes were most marked in Case 1, in which the paresis was also most severe. In Case 6 the electromyogram was normal. This patient had no clinical signs of paresis. Fig. 1 shows the appearance of the individual action potentials in Case 1. Fig. 2 shows

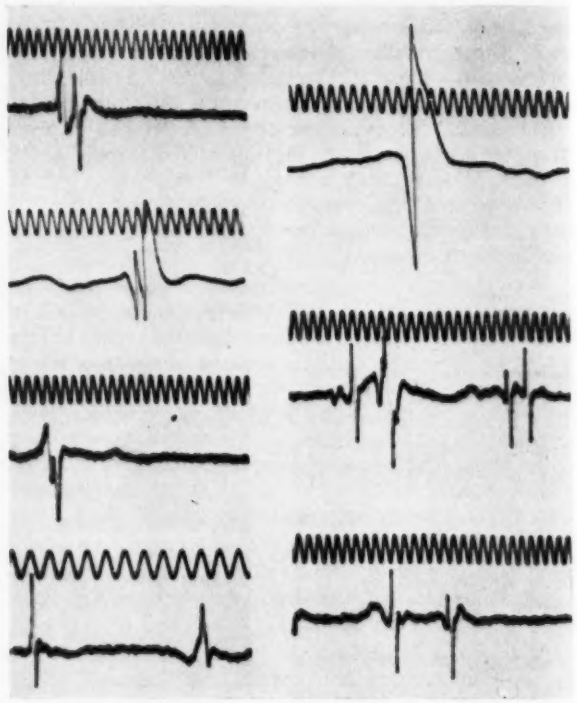

FIG. 1.—Case 1. Eleven consecutive action potentials recorded from the right quadriceps muscle. The majority have a duration of about 3 m. sec. Two polyphasic potentials are seen at the bottom right hand side. Time: 1 m. sec.

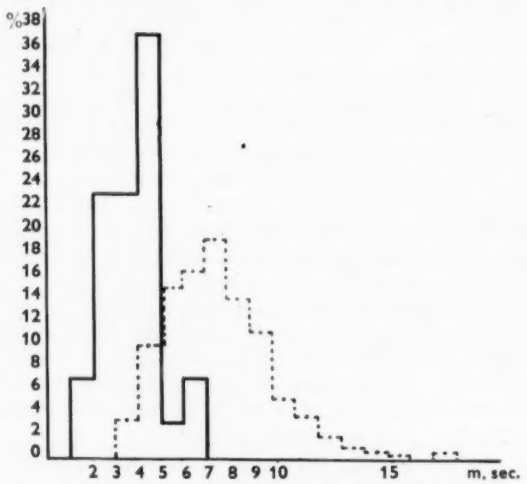

FIG. 2.—Distribution of the duration of 30 action potentials recorded from the quadriceps muscle in Case 1 (solid line) and 300 action potentials recorded from the biceps muscle in healthy individuals (broken line).

FIG. 3

FIG. 4

FIG. 5

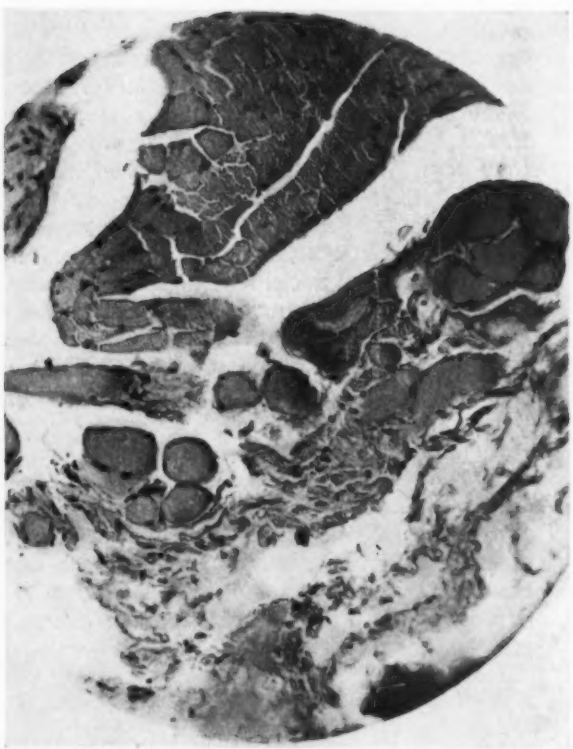

FIG. 6

FIG. 3.—Case 4. Section of biopsy from quadriceps muscle. Scattered large as well as small degenerated fibres. A few sarcolemmal nuclei are centrally placed. Heidenhain-Van Gieson. × 200.

FIG. 4.—Case 4. Section of biopsy from quadriceps muscle. A solitary swollen, hyalinized fibre at the edge of a bundle of normal muscle fibres is separated from adjacent normal muscle bundles by an increased amount of fatty tissue. Heidenhain-Van Gieson. × 200.

FIG. 5.—Case 4. Section of biopsy from quadriceps muscle. A group of extremely thin, partially fragmented muscle fibres with increased number of sarcolemmal nuclei is seen between two groups of unaffected fibres. Hansen-Van Gieson. × 375.

FIG. 6.—Case 1. Section of a biopsy from the quadriceps muscle. Hyalinized fibres of varied size adjacent to a field of normal fibres. The connective tissue is increased. No evidence of interstitial inflammatory changes. Hansen-Van Gieson. × 135.

the duration of action potentials from the quadriceps muscle of Case 1 compared with that in normal biceps muscles (Petersén and Kugelberg, 1949). Limited studies in healthy individuals show that the duration of the action potentials in the quadriceps muscle lies within the limits of normal values for the biceps muscle.

The anterior tibial muscle in Case 1 also showed marked electromyographic changes. Slight electromyographic changes were seen in distal limb muscles which exhibited no clinical paresis, as, for example, the first dorsal interosseus of the hand in Case 3. The most pronounced changes, however, were always found in the proximal muscles of the legs, which also showed the most severe muscular weakness.

Histological Examination.—The histological picture was the same in all the four cases examined and showed pathological changes (Figs. 3 to 6).

The muscle fibres were to a small extent replaced by connective tissue and fat. The diameter of the fibres varied. The majority of the fibres were somewhat thin but had otherwise normal structure. Hypertrophic fibres were also encountered. All specimens contained degenerated fibres lying in groups or singly among normal muscle fibres. The degenerated fibres usually had a rounded contour and were hyalinized and the striation obscured. Most of them were of normal thickness or enlarged. In Case 4 foci of extremely thin, fragmented fibres were seen. Most of the sarcolemmal nuclei had retained their shape and hypolemmal position. Some were dark, small and elongated, increased in number, and sometimes arranged in longitudinal rows. Occasional nuclei had migrated centrally. In Case 4 clumps of pyknotic sarcolemmal nuclei were lying free in the connective tissue. There was no convincing evidence of regeneration. Inflammatory changes did not occur. The blood vessels and nerves were normal.

In no case were the abnormalities severe. The changes were most marked in Case 4, and least in Cases 1 and 5, in which the degree of severity was appproximately the same. Case 1, however, had the most pronounced paresis and the most distinct electromyographic changes, while in Case 4 the paresis was less pronounced and the electromyographic changes less severe.

Discussion

Five of the six patients had paresis involving primarily the muscles of the pelvic girdle and thighs. Pareses due to neurogenic lesions have been reported in endocrine disorders such as acromegaly by, among others, Woltman and Kernohan (1955). A neurogenic origin of the muscular weakness in Cushing's syndrome is improbable in view of the proximal distribution of the pareses, the absence of fasciculations, the preservation of muscle reflexes, and the intact sensibility. Neither did the electromyographic and histological studies reveal any evidence of neurogenic lesions. The cause of the muscular weakness in Cushing's syndrome probably must primarily be sought in the muscle itself. This may then be a metabolic disorder which decreases the power of contraction of the individual muscle fibres or a numerical reduction of functioning fibres in the motor units.

The electromyograms showed a decrease in the duration of individual action potentials and an increased proportion of polyphasic potentials. This pattern is characteristic of disorders in which there is a reduction in the number of functioning fibres in the motor units (Kugelberg, 1947, 1949). Such electromyographic changes are, however, not specific in the sense that they may be expected to occur in any disease in which there is disintegration of the motor units, irrespective of whether this is due to reversible functional disturbances or to morphological muscle changes (Kugelberg, 1949). On the other hand, histological examination in our cases revealed the presence of varying degrees of degeneration of the muscle fibres. Consequently, in Cushing's syndrome it is a question of a true myopathy.

The histological changes were less pronounced, however, than might be expected from the clinical and electromyographic observations. In this respect the myopathy in Cushing's syndrome resembles thyrotoxic myopathy in which severe muscular weakness is not necessarily associated with pronounced morphological changes in the muscles (Adams, Denny-Brown, and Pearson, 1953; Hed, Kirstein, and Lundmark, 1958). One explanation of the discrepancy may be that the muscular weakness in Cushing's syndrome is due in part to electrolyte disturbances. This seems less probable, however, since in our patients the pareses persisted unchanged over long periods. Neither was there any definite improvement in muscle power when treatment had resulted in partial or complete regression of the other symptoms. The discrepancy may, of course, be due to the biopsy specimens not being representative of the affected muscle. A further possibility is that the routine histological techniques used were inadequate to visualize insignificant morphological changes in fibres put out of function.

The myopathy in Cushing's syndrome may be related to the increased production of corticoids. Muscle changes have been induced in experimental animals with cortisone and A.C.T.H. (Germuth, Nedzel, Ottinger, and Oyama, 1951). In rabbits

daily administration of cortisone at a dosage of 10 mg. per kg. body weight rapidly produces varying amounts of segmental degeneration of muscle fibres which is reversible (Ellis, 1956; Glaser and Stark, 1958). Cortisone-induced myopathy cannot be prevented by the administration of potassium (Ellis, 1956).

In the cases of Cushing's syndrome studied here the clinical manifestations of myopathy showed little tendency to be reversible. Neither were there any convincing signs of regeneration of muscle fibres in the biopsy specimens. The muscle changes were considerably less pronounced than those reported in experimental cortisone myopathy which, histologically, gives the impression of being an acute myopathy.

Before treatment the patients were, roughly estimated, producing from 100 to 150 mg. of corticoids per day, *i.e.*, about 2 mg. per kg. body weight. This amount is small compared with that administered experimentally, but while the animal experiments lasted only a few weeks, the patients were exposed to the effect of increased corticoid production for years. The difference between the myopathy in Cushing's syndrome and cortisone-induced myopathy should be considered against this background.

It is known that prolonged cortisone medication in large doses may lead to severe muscular weakness (Lukens, 1954, among others). It is possible that the muscular weakness in these cases is due to myopathy of the same type as we observed in Cushing's syndrome.

Summary

In six patients with Cushing's syndrome the muscle functions have been studied clinically and electromyographically. Muscle biopsy was done in four of them.

Five patients had weakness of the proximal muscles of the lower limbs; two of them had, in addition, weakness of the shoulder girdle muscles and of the dorsiflexors of the feet. The paresis was most pronounced in the proximal muscles of the lower limbs. Only in one case was the paresis severe; in the other four it was moderate or slight. One patient had no muscular weakness.

In three of the patients the muscular weakness appeared several years after the onset of the disease, when the other symptoms had become severe. After successful treatment of the Cushing syndrome the muscular weakness persisted unchanged for years in two cases; in one case there was a slight increase of muscular power.

The electromyographic examination in the five patients with paresis revealed signs of myopathy, most pronounced in the muscles that were clinically weakest. Changes of the myopathic type were also observed in distal limb muscles which clinically were completely normal.

The histological changes consisted of slight or moderate degeneration of muscle fibres. The intensity of the changes was less than might be expected from the clinical and electromyographic observations.

It is concluded that the muscular weakness in Cushing's syndrome is due to a true myopathy, probably produced by the increased production of corticoids.*

We are indebted to Professor Nils Antoni and Assistant Professor Karl Erik Åström for the histological examinations.

References

Adams, R. D., Denny-Brown, D., and Pearson, C. M. (1953). *Diseases of Muscle*. Hoeber, New York.
Cushing, H. (1932a). *Bull. Johns Hopkins Hosp.*, **50**, 137.
—— (1932b). *J. Amer. med. Ass.*, **99**, 281.
Ellis, J. T. (1956). *Amer. J. Path.*, **32**, 993.
Germuth, F. G., Nedzel, G. A., Ottinger, B., and Oyama, J. (1951). *Proc. Soc. exp. Biol. (N.Y.)*, **76**, 117.
Glaser, G. H., and Stark, L. (1958). *Neurology*, **8**, 640.
Hed, R., Kirstein, L., and Lundmark, C. (1958). *J. Neurol. Neurosurg. Psychiat.*, **21**, 270.
Kugelberg, E. (1947). *Ibid.*, **10**, 122.
—— (1949). *Ibid.*, **12**, 129.
Lukens, F. D. W. (1954). *Medical Uses of Cortisone*. Blakiston, New York—Toronto.
Marburg, O. (1933). *Arb. neurol. Inst. Univ. Wien.*, **35**, 143.
Petersén, I., and Kugelberg, E. (1949). *J. Neurol. Neurosurg. Psychiat.*, **12**, 124.
Soffer, L. J. (1951). *Diseases of the Endocrine Glands*. Lea & Febiger, Philadelphia.
Woltman, H. W., and Kernohan, J. W. (1955). In Baker, A. B., *Clinical Neurology*, Vol. 3, p. 1563. Hoeber, New York.

* After this paper was sent in for publication another patient with an untreated Cushing's syndrome, who exhibited much more severe myopathic changes, was seen in the Clinic.

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SOME MUSCULAR MANIFESTATIONS OF HYPOTHYROIDISM

BY

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Although it has been recognized for many years that symptoms and signs indicating disordered function of the voluntary musculature may be prominent in patients with myxoedema, the muscular manifestations of hypothyroidism have received comparatively little attention in the British literature. Recent reviews have, however, been given by Thomasen (1948), Piaggio Blancho and Malosetti (1950), Millikan and Haines (1953), Herbeuval, Cuny, and Larcan (1956), Dubanský, Svoboda, and Wiedermann (1957), and Perugini and Prati (1957).

Kocher (1892) reported that patients with sporadic cretinism or myxoedema often showed bulky musculature, diminished muscular power, and sluggish movement with or without "tetany". Hoffmann (1897) later described features suggestive of myotonia in a patient who had undergone thyroidectomy several times ; he pointed out that in this case there was a striking delay in muscular relaxation, reminiscent of that which occurs in myotonia congenita (Thomsen's disease). Since these early descriptions the syndrome of generalized muscular hypertrophy with sluggishness of muscular contraction and relaxation, which occurs in myxoedematous adults, has been referred to as "Hoffmann's syndrome". A similar disorder seen in cretinous infants is generally called the "Debré-Semelaigne syndrome". Probably this disorder accounts for many cases of so-called acquired myotonia or myotonia acquisita (Talma, 1892). In fact, however, the abnormality of muscle function which results from hypothyroidism must be distinguished from true myotonia, as the overall slowness of muscular activity affects muscular contraction as well as relaxation and the typical electrical after-discharge of myotonia is not seen. Hence the term "pseudomyotonia" is a more appropriate description for the myxoedematous phenomenon.

Whereas it is not difficult in patients with florid myxoedema to appreciate that slowness of movement and stiffness of the voluntary muscles may be attributable to the thyroid disease, particularly when there is also marked muscular hypertrophy, we have been impressed by the fact that the muscular symptoms may not always follow the accepted form and may be the presenting feature in patients in whom hypothyroidism is otherwise clinically unobtrusive. We report below three cases in which diagnosis presented considerable difficulty but nevertheless the response to treatment was rapid and sustained.

Case Reports

Case 1.—M.E., an anxious, hypochrondriacal housewife, born in 1919, began in 1953 to complain of intolerance of heat, profuse sweating, and loss of weight. A smooth enlargement of the thyroid gland had been present for 10 years. She was found to have warm, moist palms, tachycardia of 108/ min., and blood pressure of 165/85 mm. Hg. The B.M.R. was + 23%. For the next two years the patient was treated in turn with neomercazole, Lugol's iodine, and methyl thiouracil in an unsatisfactory attempt to achieve control of the thyrotoxic symptoms. A subtotal thyroidectomy was eventually performed by Professor A. G. R. Lowdon at the end of September, 1955. Immediately after the operation there was a mild thyrotoxic crisis, but she made sufficiently rapid progress post-operatively for her to be discharged home six days after operation. In November, 1955, the patient complained that her fingers and facial muscles had been stiff since her return home, and her face slightly swollen. At that time she was thought to be euthyroid. In early 1956 she was referred to a psychiatrist because of a complaint of bizarre aches and pains affecting all limbs. No psychological cause for the patient's symptoms was evident but no satisfactory alternative explanation was offered. She was seen again by a physician who mentioned that although she had gained 3 stones in weight post-operatively, there were no clinical signs of hypothyroidism. As the muscular pain and aching persisted the patient was referred to one of us (J.N.W.). It was then observed that there was generalized muscular hypertrophy which was especially marked in the quadriceps and calves. All the voluntary muscles were stiff and felt indurated ; movements were slowly performed and on percussion of the deltoids and quadriceps there was " dimpling " of the muscle, lasting for over two seconds, and similar to that seen in myotonia. Although the pulse rate was 90/min., the skin felt cold, the patient was lethargic, constipated, and looked mildly myxoedematous. She refused readmission

o hospital for investigation ; in view of a presumptive linical diagnosis of Hoffman's syndrome, she was treated vith tri-iodothyronine, 40 μg daily. When next seen one veek later she was asymptomatic and composed. All he muscular pain and stiffness had disappeared. Within few weeks the muscular hypertrophy was much less vident. In June, 1958, dried thyroid extract, grains daily, was satisfactorily substituted for tri-iodo-hyronine ; the patient has remained well since.

The clinical picture in this case was characteristic of Hoffmann's syndrome and the therapeutic response to tri-iodothyronine, and later to thyroid extract, was prompt and sustained.

Case 2.—R.N., a health visitor, was born in 1917. In 1944 she underwent a partial thyroidectomy for toxic goitre. Almost immediately following this operation she began to complain of aches and pains in all her limbs after exertion, like an "after-tennis feeling". These symptoms persisted in a degree insufficient to interfere with her work. In April, 1957, having swallowed a fish-bone, she had an oesophagoscopy under a general anaesthetic and the bone was removed. During anaesthesia intravenous succinylcholine was used ; the patient recovered normally from the anaesthetic but next day all her limbs became completely paralysed and flaccid. This severe weakness persisted for 24 hours and then slowly remitted over the following week. In May, 1957, after several attacks of renal colic she had a nephrectomy for hydronephrosis due to an aberrant artery. Succinylcholine was again used, and on this occasion, flaccid paralysis of the limbs was present immediately after the operation and again persisted for 24 hours. During both periods of paralysis there was slight dysphagia and dysarthria but no respiratory embarrassment. Serum potassium determinations during each attack of paralysis were normal and there was no response to prostigmine. In December, 1957, the patient was referred to one of us (J.N.W.) as a possible case of polymyositis, as by now the generalized muscular aching and pains in the limbs were more severe. For the first hour after rising in the morning she would feel well and symptom-free, but then progressively throughout the day she would become slower and easily fatigued ; she had particular difficulty in climbing stairs. When tired, the "after-tennis feeling" in the muscles was particularly troublesome. Because of an increase in these symptoms, she was by this time unable to follow her occupation as a health visitor.

On examination there were no clinical abnormalities ; in particular there was no muscular wasting, weakness, tenderness, or hypertrophy, and no clinical myotonia could be demonstrated, either on relaxation of the grip or on percussion of muscles. The tendon reflexes were symmetrically brisk and the plantar responses were both flexor. The patient appeared to be euthyroid.

Investigations.—The following investigations were carried out :—

Blood.—Haemoglobin 13.9 g./100 ml., W.B.C. 6,500/c. mm. (differential count normal), E.S.R. 5 mm. in one hour (Westergren), plasma sodium 138 mEq./litre, plasma potassium 4·6 mEq./litre, serum calcium 9·6 mg./100 ml., plasma phosphate 2·4 mg./100 ml., total serum proteins 7·2 g./100 ml. (albumin 4·9 g./100 ml., globulin 2·3 g./100 ml.), serum cholesterol 255 mg./100 ml., fasting blood sugar 76 mg./ml.

Using the tanned red cell technique (Owen and Smart, 1958), Dr. S. G. Owen demonstrated circulating antibodies to thyroglobulin in the venous blood to a dilution of 1 in 675.

Urine.—No albumin or reducing substances were detected and no abnormal deposit was found on microscopy.

The creatinine level was 1·57 g. in 24 hours and the creatine 0·03 g. in 24 hours.

The basal metabolic rate was +2% and an I^{131} uptake test was well within normal limits. An electrocardiogram was normal and a muscle biopsy taken from the left deltoid yielded a specimen in which no significant histological change could be detected. After the administration of insulin and glucose the serum potassium fell to 3 mEq./litre but no muscular weakness could be demonstrated.

Electromyography.—Electromyograms were recorded, using concentric needle electrodes, from the left deltoid, the left biceps brachii, and the right quadriceps. No spontaneous activity was recorded ; in particular, there was no fibrillation and no myotonic discharges were obtained on moving the electrode. Volitional activity was also normal ; no excess of polyphasic or short-duration potentials was recorded.

Treatment.—The patient was treated initially with lactose control tablets but her symptoms remained unchanged. The administration of tri-iodothyronine in a daily dosage of 40 μg. was followed by prompt remission of symptoms and a feeling of well-being. During succeeding weeks, all muscular pain and weakness vanished, the patient became energetic and symptom-free, and was able to return to her previous occupation. After six months' treatment with tri-iodothyronine, dried thyroid extract, 3 grains daily, was begun, and two weeks later, tri-iodothyronine was withdrawn. In another two weeks the muscular pain and aching had returned. Owing to increasingly severe symptoms, tri-iodothyronine was again given, with prompt and sustained remission and the patient has remained well for one year, taking 40 μg. of this drug daily.

In this case there was no clinical evidence of hypothyroidism, apart from the muscular symptoms, and all investigations of thyroid function were normal, save for the discovery of antibodies to thyroglobulin, a finding suggesting a previous thyroiditis (Hashimoto disease). The relapse on treatment with thyroid extract suggests either that the particular batch of tablets was inactive or that there was a defect in the breakdown of thyroxin to tri-iodothyronine. The episodes of paralysis following succinylcholine suggest an unusual sensitivity of the muscle fibre membrane to this drug ; but the relationship to hypothyroidism and the reason

for delay in the development of the first episode of weakness are not apparent.

Case 3.—E. T., a housewife, was born in 1917. In 1950, after two years of breathlessness, palpitations, sweating, tremor, and loss of weight, she underwent a partial thyroidectomy ; a small nodular goitre was discovered. Her symptoms persisted and in 1954 a further partial thyroidectomy was performed. Once more her symptoms were unchanged and yet another operation to remove remaining thyroid tissue was carried out in 1955.

Three months after this operation the patient began to experience several attacks each day in which she experienced painful cramps affecting mainly the left forearm and hand, each lasting one or two minutes. These attacks could be provoked by exercise and were often accompanied by superficial tingling. The right hand was similarly though mildly affected. About one month later similar cramps developed in both legs. Since the cramps resembled the carpopedal spasms of tetany, repeated serum calcium and phosphate estimations were performed, but all were normal. The patient was then referred to one of us (J. N. W.). She mentioned that her appetite was poor, she was losing weight, and was very constipated. Since her last operation she had felt cold, her skin was dry, and her hair falling out. Her muscles had also felt stiff and painful and all movement was slower than it had been previously.

On examination the patient was thin and nervous ; despite her complaints of feeling cold her palms were warm and moist, but the pulse rate was 72/min., the blood pressure 115/80 mm. Hg. There was no residual palpable thyroid swelling. Some brown pigmentation was present around the neck, on the forearms and iliac crests. In the limbs, although all the muscles were thin, there was no localized muscular atrophy, tenderness, or weakness. There was, however, marked delay in relaxation of the grip, resembling myotonia, and persistent dimpling of the muscle was present after percussion. The consistency of the muscles appeared to be increased and there was an increased resistance to passive stretching throughout, but no hypertrophy was evident. All the tendon reflexes were brisk, without any evidence of delay in muscular contraction or relaxation ; the abdominal reflexes were present and the plantar responses flexor. On application of a tourniquet to the left upper limb, a spasm of the left hand, very reminiscent of tetany, was produced. Chvostek's sign was negative. It was felt that although many of the patient's symptoms were those of a chronic anxiety state, there was definite evidence of hypothyroidism which was probably the explanation of the symptoms referrable to the voluntary muscles.

Investigations.—The following investigations were carried out :—

Blood.—Haemoglobin 11·6 g./100 ml., white cell count 9,800/c. mm. (differential count normal), E.S.R. 1 mm. in one hour (Westergren), plasma sodium 138 mEq./litre, plasma potassium 4·1 mEq./litre, serum calcium 9·2 mg./100 ml., plasma phosphate 2·5 mg.P. /100 ml., total serum proteins 5·8 g./100 ml.

Urine.—No albumin or reducing substance was detected.

In two specimens urinary 17-ketosteroids were 1·2 mg. and 1·5 mg./24 hours respectively. The B.M.R. was −4%.

The uptake of I^{131} was in the hypothyroid range ; 4·8% of initial dose at 1·5 hours ; 5·3% at 4 hours ; 12·4% at 26 hours, and 10·8% at 49·5 hours.

Thorn's test over 48 hours showed normal depression of the blood eosinophil count.

Electromyography.—Electromyograms recorded from the left deltoid, the left forearm, and the left quadriceps with concentric needle electrodes were entirely normal. No myotonic discharges were recorded.

Treatment.—Procaine amide, in a dosage of 750 mg. four times daily, was given initially with a considerable reduction in muscular stiffness and improved relaxation, but the painful cramps persisted. Thereafter tri-iodothyronine, 20 μg. twice daily, was given. Within a few days, all muscular pain and stiffness had disappeared and the carpopedal spasms were greatly reduced in frequency and severity. After a few weeks of treatment these symptoms were no longer prominent and the patient returned to normal activity. Anxiety symptoms such as palpitations, malaise, and excessive sweating persisted intermittently and presented considerable difficulties in subsequent management. On two occasions over the next three years tri-iodothyronine therapy was discontinued but on each occasion muscular pain and stiffness and painful cramps recurred. The clinical picture is now dominated by anxious hypochondriasis, but muscular symptoms are no longer prominent. Further investigation has revealed no evidence of hypopituitarism or of Addison's disease.

In this case, the coexistence of a severe chronic anxiety state led to considerable difficulties in both diagnosis and management. Muscular pseudo-hypertrophy was not present and the carpopedal spasms favoured a diagnosis of hypoparathyroidism, although no abnormality of calcium and phosphorus metabolism could be demonstrated. The muscular pain and stiffness was, however, suggestive of hypothyroid myopathy and the I^{131} uptake test was diagnostic of hypothyroidism. The muscular symptoms resolved after treatment with tri-iodothyronine.

Discussion

These three cases have in common the following features :—

(a) In each, symptoms followed thyroidectomy.

(b) The symptoms and signs of muscular dysfunction and those of hypothyroidism remitted, usually completely, on treatment with tri-iodothyronine. For this reason and because the clinical features in each case resemble some of those previously described in hypothyroidism, it appears that the muscular symptoms could be attributed to a deficiency of thyroid hormone. The muscular

disorders which have been described in association with hypothyroidism are, according to Thomasen (1948) and Perugini and Prati (1957) :—

(1) A myotonoid syndrome (pseudomyotonia, myotonia acquisita).

(2) Muscular hypertrophy in adults, with firm, often painful muscles ; power and tone are variable, and both contraction and relaxation are usually sluggish.

(3) Muscle hypertrophy with reduced or increased power in infants suffering from sporadic cretinism, giving the appearance of "the infant Hercules", the Debré-Semelaigne syndrome (Debré and Semelaigne, 1935).

(4) Muscle cramps, which sometimes resemble classical tetany.

(5) Rare atrophic forms (Canali, 1941 ; Nick, 1943 ; Rimbaud and Passouant, 1947 ; Piaggio Blancho and Malosetti, 1950).

These phenomena may occur singly or in any combination, and may be of varying severity. They have been described in patients after total (Hoffmann, 1897) and partial thyroidectomy (Crispell and Parson, 1955 ; Hofman-Credner, 1956), after I^{131} in ablation doses (Gilbert-Dreyfus, Zara, and Gali, 1954), after radiotherapy (Lenègre and Huguenin, 1941), after "lipiodol" (Sigmir, quoted by Herbeuval *et al.*, 1956), in so-called "spontaneous" myxoedema (Thomasen, 1948), in hypothyroidism secondary to hypopituitarism (Dubanský *et al.*, 1957), and in sporadic cretinism (Debré and Semelaigne, 1935).

The mechanism of these muscular symptoms is unknown, and we have no satisfactory explanation for their patho-physiology ; in particular it cannot be explained why only a proportion of patients with myxoedema are so affected. To describe the changes as "myxoedema of the muscles" does not contribute anything to our understanding of the condition, and definitive metabolic studies of muscular function in such cases are lacking.

Pseudomyotonia at first sight resembles true myotonia in that there is delayed relaxation of the grip, worse in cold weather ; the phenomenon is, however, quite different. It is apparent that in these cases muscular contraction as well as relaxation is slowed, and the characteristic after-discharge of myotonia is absent electromyographically, as are the typical bizarre insertion discharges associated with the latter phenomenon. Direct percussion of affected muscle does, however, produce a local dimpling as in true myotonia. The response to quinine in pseudomyotonia is said to be poor, though Crispell and Parson (1955) claim a good response in one patient ; it is of interest that in our Case 3, there appeared to be a definite improvement with procaine amide, a remedy which relieves myotonia (Geschwind and Simpson, 1955 ; Leyburn and Walton, 1959).

Muscular hypertrophy may be generalized or localized, predominantly affecting the calves and thighs, although the facial muscles can also be markedly involved. Muscle power is usually decreased, despite the hypertrophy, and the movements are usually sluggish, sharing in the general torpor of the myxoedematous patient. Increase of power has, however, been described, especially in the Debré-Semelaigne syndrome. The so-called Woltman tendon reflex in such cases, which depends upon the demonstration of an unusual slowness of muscular contraction and relaxation when the knee jerk is being elicited, may be of considerable diagnostic value (Chaney, 1924 ; Lambert, Underdahl, Beckett, and Mederos, 1951).

Muscular pain and cramps are usually seen in those patients with enlarged, brawny muscles but can occur in others, even when there is no other clinical evidence of hypothyroidism. Muscular pain on exertion, as in cases of so-called myotonia paradoxa, and resembling also in some respects the symptoms of McArdle's myopathy due to a defect in muscle glycogen breakdown (McArdle, 1951), may be the outstanding clinical feature, as in our Case 2. Symptoms suggesting classical tetany may also be seen, as in Case 3.

The atrophic form may resemble the more familiar muscular dystrophies (Piaggio Blancho and Malasetti, 1950) but several of the reported cases are not well attested and there may have been alternative explanations for the muscular atrophy (Rimbaud and Passouant, 1947 ; Dubanský *et al.*, 1957).

These variable clinical phenomena may give rise to considerable difficulty in diagnosis, especially if the usual clinical features of myxoedema are unobtrusive ; it is only too easy for symptoms of this nature, for which no ready explanation is forthcoming, to be dismissed as being psychogenically determined. In our Cases 1 and 3 the symptoms were at different times attributed by several observers to hysteria or anxiety while in Case 2 a diagnosis of endogenous depression was at one time entertained. It is important to emphasize that there is no parallel between the degree of hypothyroidism and the severity of the muscular symptoms and signs, nor do the latter present a consistent clinical picture. Diagnosis may depend on a "high index of suspicion ". A low basal metabolic rate, high serum cholesterol level, reduced I^{131} uptake, and low protein-bound iodine may afford confirmation of the diagnosis but the results of these tests may be only slightly abnormal (*myxoedema frustes* of

French writers) ; indeed they may even be normal as in our Case 2, in which the diagnosis finally depended upon the finding of a raised titre of antibodies to thyroglobulin in the patient's serum, as well as upon the therapeutic test.

Unlike the usual findings in myotonia congenita and paramyotonia, in which the electrical phenomena may represent a recurring excitation of muscle fibres, the electromyogram in myxoedematous pseudomyotonia is usually normal. Pseudomyotonia therefore, is probably due to a delay in relaxation of individual muscle fibres after a single excitation, and may represent an abnormally slow release of energy from the energy-rich bonds within the muscle cell, as a part of a general reduction in metabolic rate. Electrical stimulation of myxoedematous muscles may provoke a myotonoid reaction but strength-duration curves from these muscles are usually normal or show only a slightly increased chronaxie (Bourguignon, 1939 ; Picard, Horeau, Kerneis, Lhermitte, and Lescaudron, 1955 ; Svoboda, Dubanský, and Myslivý, 1956). Muscle specimens removed by biopsy, even from hypertrophied muscle, are usually normal, as in our Case 2. Picard *et al.* (1955) found "hypertrophy" of sarcoplasm, accentuation of both longitudinal and transverse striation, coexistence of both hypertrophic and atrophic fibres, and increased numbers of sarcolemmal nuclei in material from their cases, but these descriptions are not entirely convincing. Inflammatory changes, fatty infiltration, and fibrosis have not been described. Thomasen (1948) believed that the muscle hypertrophy was not due to genuine hyperplasia or hypertrophy of the fibres, but to oedema. Hesser (1940) has put forward the interesting, but as yet unconfirmed, view that the hoarseness which is so striking a feature of myxoedema is due in part to hypertrophy of the laryngeal muscles and that the deafness which occasionally occurs depends upon enlargement of the intrinsic musculature of the ear.

In the last resort, diagnosis depends on the complete remission of symptoms with thyroid extract or more dramatically with tri-iodothyronine. It is difficult to explain why symptoms in Case 2 should have responded to tri-iodothyronine and not to thyroid extract. Either the batch of thyroid extract utilized was inactive (which seems unlikely) or else in this case there was some derangement of the metabolic mechanism whereby absorbed thyroxin is converted into tri-iodothyronine within the body.

The exact incidence of muscular complications of hypothyroidism has never been estimated, and although the three patients in the present report were female, there does not appear to be a genuine sex difference. We suspect that these muscular manifestations are more frequent than is generally realized, minor degrees being overlooked in florid myxoedema, or wrongly ascribed to other causes such as intermittent claudication (Ericsson and Lindquist, 1945). Myxoedematous myopathy should certainly be considered as a possibility in all patients who complain of generalized muscular pain, aching or stiffness, particularly if this develops after exertion.

Summary

Three cases are described in which symptoms indicating disordered function of the voluntary musculature were prominent ; these symptoms, which included muscular pain and stiffness, accentuated by exertion, and in one case painful cramps resembling tetany, were shown to be due to hypothyroidism, and responded to treatment with tri-iodothyronine. In each case, the other symptoms of hypothyroidism were relatively unobtrusive.

The clinical features of myxoedematous pseudomyotonia, and its differentiation from true myotonia, are discussed. The view is expressed that this condition is more common than is generally realized, and should be borne in mind as a possible diagnosis in all patients complaining of generalized muscular pain and stiffness.

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References

Bourguignon, G. (1939). *Rev. neurol.*, **71**, 548.
Canali, G. (1941). *Riv. clin. med.*, **42**, 301.
Chaney, W. C. (1924). *J. Amer. med. Ass.*, **82**, 2013.
Crispell, K. R., and Parson, W. (1955). *Trans. Amer. Goiter Ass.*, 1954, 399.
Debré, R., and Semelaigne, G. (1935). *Amer. J. Dis. Child.*, **50**, 1351.
Dubanský, B., Svoboda, E., and Wiedermann, M. (1957). *Nervenarzt*, **28**, 61.
Ericsson, E., and Lindquist, T. (1945). *Acta med. scand.*, **121**, 132.
Geschwind, N., and Simpson, J. A. (1955). *Brain*, **78**, 81.
Gilbert-Dreyfus, Zara, M., and Gali, P. (1954). *Presse méd.*, **62**, 1553.
Herbeuval, R., Cuny, G., and Larcan, A. (1956). *Rev. méd. Nancy*, **81**, 1010.
Hesser, F. H. (1940). *Bull. Johns Hopk. Hosp.*, **66**, 353.
Hoffmann, J. (1897). *Dtsch. Z. Nervenheilk.*, **9**, 278.
Hofmann-Credner, D. (1956). *Wien. Z. inn. Med.*, **37**, 197.
Kocher, T. (1892). *Dtsch. Z. Chir.*, **34**, 566.
Lambert, E. H., Underdahl, L. O., Beckett, S., and Mederos, L. O. (1951). *J. clin. Endocr.*, **11**, 1186.
Lenègre, J., and Huguenin, R. (1941). *Bull. Soc. Méd. Hôp. Paris*, 3rd series, p. 650.
Leyburn, P., and Walton, J. N. (1959). *Brain*, **82**, 81.
McArdle, B. (1951). *Clin. sci.*, **10**, 13.
Millikan, C. H., and Haines, S. F. (1953). *Arch. intern. med.*, **92**, 5.
Nick, J. (1943). *Les atrophies myopathiques liées à l'insuffisance thyroïdienne acquise de l'adulte*. Thèse de Paris. Quoted by Perugini and Prati (1957).
Owen, S. G., and Smart, G. A. (1958). *Lancet*, **2**, 1034.
Perugini, S., and Prati, P. L. (1957). *Med. int. (Milano)*, **65**, 24.
Piaggio Blancho, R. A., and Malosetti, H. (1950). *Arch. urug. Med.*, **37**, 341.
Picard, R., Horeau, J., Kerneis, J., Lhermitte, R., and Lescaudron, A. (1955). *Sem. Hôp. Paris*, **31**, 1553.
Rimbaud, L., and Passouant, P. (1947). *Rev. neurol.*, **79**, 81.
Svoboda, E., Dubanský, B., and Myslivý, M. (1956). *Čas. Lék. Čes.*, **95**, 912.
Talma, S. (1892). *Dtsch. Z. Nervenheilk.*, **2**, 197.
Thomasen, E. (1948). *Myotonia*. Copenhagen.

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HISTOCHEMICAL DISTRIBUTION OF PHOSPHORYLASE IN THE BRAIN OF THE GUINEA-PIG

BY

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The histochemical distribution of phosphorylase activity in brain tissue of rodents was described by Shimizu and Okada (1957) using fresh, frozen tissue sections. The present article describes the distribution of phosphorylase activity in the brain of the guinea-pig as revealed by using tissue slices trimmed by hand instead of sections for incubation (Friede, 1956). This technique provides an improved localization of phosphorylase activity. The preparation of tissue for incubation seems to be a critical phase of the reaction since changes in the enzyme activity result from tissue damage (Friede, 1959a).

The distribution of phosphorylase in brain tissue as defined by this technique will be compared briefly with an available large sampling of the distribution of succinic dehydrogenase in brain tissue. An inverse relationship between the two enzymes would be conceivable, considering the former one as a link of the anaerobic glycolytic breakdown and the latter as an indication of the presence of an oxidative Krebs cycle.

Material and Methods

Phosphorylase activity was demonstrated in 0·5 to 1 mm. thick hand-cut tissue specimens prepared from the brain as quickly as possible after killing the animal. Extreme care was used to prevent any mechanical damage to the tissue. The specimens were incubated for three hours at 36° to 38° C. in the following medium:

Glucose-l-phosphate ..	6%
Glycogen	0·1%
Adenosinetriphosphate ..	1%
Mono iodacetate	0·25%

During the incubation, glycogen was synthesized from Cori ester; the added glycogen served as a starter of the reaction, but its concentration was too low to appear histochemically in the sections. No pre-existing glycogen could be found in brain tissue under these conditions. Mono iodacetate essentially improved the reaction by blocking the glycolytic breakdown of the Cori ester. Adenosinetriphosphate (or adenylic acid) activates phosphorylase (Takeuchi and Kuriaki, 1955). The solution adjusted itself to a *p*H of 7·0, and the addition of buffer to obtain the optimal *p*H or of inorganic ions did not essentially influence the results. Glucose and phlorhizin inhibited the reaction. No glycogen was synthesized by substituting the Cori ester with glucose-6-phosphate, glucose, fructose-6-phosphate, or fructose-1,6-diphosphate.

After the reaction was completed the specimens were fixed in Carnoy's fluid and embedded in paraffin. Glycogen was demonstrated by the periodic-acid-Schiff reaction; it was identified by diastase controls.

Some 130 incubations were used for the present investigation, each containing at least three specimens from various regions of the brain. In addition, one guinea-pig brain was studied completely by serial sections, 12μ thick. Alternate sections were stained with periodic-acid-Schiff, Einarson's chromalum gallocyanin, and a combination of both stains.

Results

White Matter.—White matter generally exceeded grey matter in phosphorylase activity. The axons in the white matter were demonstrated and found to give an intense phosphorylase reaction. A granular reaction between the axons was also found. Most of these granules seemed to result from varying intensity of the reaction in the axons or from transversally cut axons. Phosphorylase activity was rarely localized in glial cells although it should be easy to recognize it at this site. The phosphorylase activity of white matter, therefore, seemed predominantly localized in the axons.

The phosphorylase activity of large fibre systems was more marked than that of the surrounding tissue; for example, the pyramidal tracts, the descending trigeminal root, the lateral tracts of the medulla oblongata, and the entire cerebral and cerebellar white matter showed strong activity. The medial longitudinal fascicle exhibited phosphorylase activity in its large axons. By contrast, the tractus solitarius always stood out by the negative reaction of its surrounding nucleus. The roots of the cranial nerves and the optic fascicle exhibited strong phosphorylase activity in their large axons. A very strong reaction was found in the retroflex tract of Meynert.

Gray Matter.—The inconsistency of the phosphorylase reaction in neurones was studied in a previous article (Friede, 1959a). Strong phosphorylase activity was found in the chromophilic, shrunken neurons; however, no activity was found in the swollen, chromatin-depleted neurons. Since these neuronal changes evidently were post-mortem changes, the significance of a positive reaction is open to discussion.

In the present material, neurons with strong phosphorylase reaction were found irregularly and scattered in almost any nucleus; they were frequently found in damaged tissue portions near the surface of the specimen.

The neuropil of the brain's nuclei, as a rule, lacked phosphorylase activity, especially if mechanical damage was minimized during preparation. This negative reaction of the neuropil did not result from inadequate diffusion of the incubation medium into the specimen, since transfixing axons were sharply outlined by a contrasting strong reaction. A delicate network, demonstrated by phosphorylase activity, was occasionally found in the neuropil. It could not be established whether this reticulum was formed by finer axon or dendrite branchings or by glial processes, but the latter seemed less probable. Phosphorylase activity in glial cells may occasionally be found in gray matter, but did not constitute a typical feature. Gray matter exposed to mechanical damage, such as at the cutting surface, showed very strong phosphorylase activity by abundant glycogen deposition. Other nuclei immediately beneath the specimen's surface showed no reaction if not injured by the cutting. The diffusion conditions in such nuclei, however, were similar to those at the cutting surface, as proven by the heavy reaction in transfixing axons.

The above description fits most of the nuclei of the medulla oblongata, pons, mesencephalon, and diencephalon. Weak phosphorylase activity was particularly found in the dorsal vagal nucleus, the nucleus of the tractus solitarius, the locus caeruleus, and the pars compacta of the substantia nigra. These nuclei are mentioned because of their comparative histochemical interest as discussed later.

Some superficial nuclei, such as the nucleus prepositus hypoglossi, the medial vestibular nucleus, the cochlear nucleus, and the mammillary body, frequently, but not consistently, exhibited strong phosphorylase activity in their neuropil. Both exposure to mechanical damage during preparation and optimal diffusion conditions may contribute to this reaction.

Phosphorylase activity was consistently found in the molecular layer of the cerebellar cortex, the superficial layers of the acoustic tubercle, and the anterior quadrigeminal body, the upper layers of the cerebral cortex, and the caudate nucleus. The cerebellar cortex exhibited phosphorylase activity in the neuropil and in the large Purkinje dendrites of its molecular layer, but the reaction in the dendrites disappeared where they entered the cell body. Thus most of the cell bodies reacted negatively, but some of them showed strong phosphorylase activity. Weak activity was found in the cerebellar granular layer. The interpeduncular ganglion and the habenula showed in their neuropil the strongest reaction of all the brain's nuclei.

It is not clear whether this consistent phosphorylase reaction in some nuclei reflects activity *in vivo* or if these regions are extremely sensitive to damage and should show no phosphorylase reaction as other nuclei do if completely undamaged.

The periventricular gray matter of the aqueduct and the tuber cinereum frequently exhibited phosphorylase activity in astrocytes besides a diffuse granular reaction of the neuropil. No other region of the brain regularly showed phosphorylase activity in glial cells, though it was found at times.

Ventricular Walls and Leptomeninges.—A very strong phosphorylase activity was found in the subependymal glial tissue. Contrasting with this strong subependymal reaction, the ependymal cells lacked phosphorylase activity although in direct contact with the incubation fluid. Some glycogen droplets, however, were frequently found in the ventricular lumen, attached to the surface of the ependymal cells. Since synthesis of glycogen in this location did not seem likely, this finding may suggest a supravital transportation or secretion. The epithelium of the subcommissural organ, which is a specific ependymal formation in the aqueduct, completely lacked phosphorylase activity, but the glial tissue of the raphe immediately caudal to it exhibited an excessive reaction. The area postrema exhibited strong or mild activity. Somewhat variable strong to mild activity was also found in the leptomeninges.

Comparison of Distribution of Phosphorylase and Succinic Dehydrogenase.—Dempsey and Wislocki (1944) and Bradfield (1951) suggested that glycogen deposition in tissue was correlated with a high anaerobic metabolism. An inverse relationship between the distribution of glycogen deposition and the distribution of succinic dehydrogenase and cytochrome oxidase in the periventricular structures of the brain was observed by Shimizu, Morikawa, and Ishi (1957). The above findings, therefore, were compared with an available large sampling of the distribution of succinic dehydrogenase in brain tissue of the guinea-pig (Friede, 1959b). Succinic dehydrogenase was demonstrated in this material in

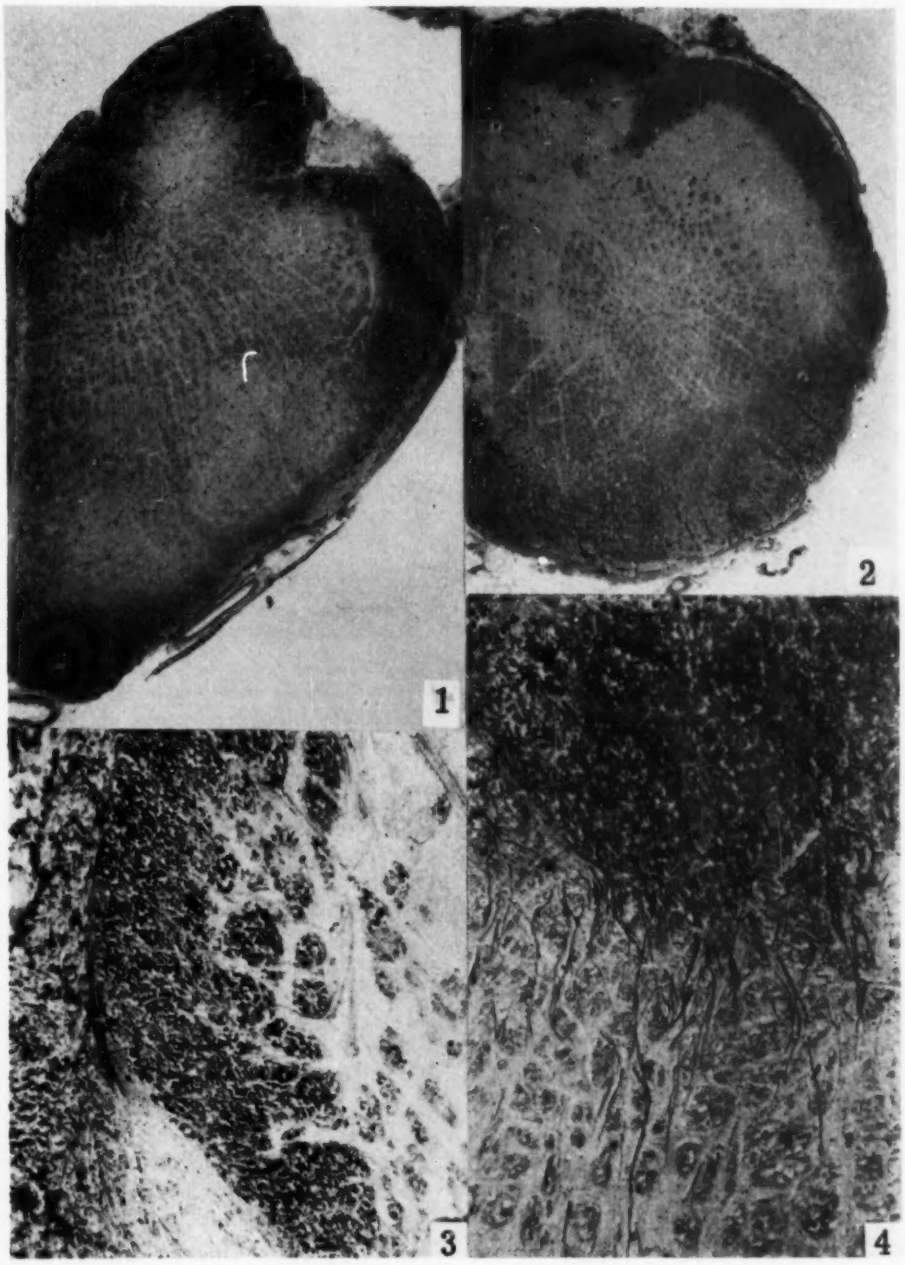

FIG. 1.—Distribution of phosphorylase activity in the medulla oblongata. The lateral vestibular nucleus, the nucleus of the descending trigeminal tract, and the facial nucleus stand out as light areas. Periodic-acid-Schiff × 16.

FIG. 2.—Lower medula oblongata, showing a negative reaction in the nuclei of the dorsal fasciculi and the spinal trigeminal tract and a very faint reaction in the hypoglossal nucleus. The space of the facial nucleus (Fig. 1) is occupied by heavily reacting fibre tracts. Periodic-acid-Schiff × 16.

FIG. 3.—Descending trigeminal root (middle). Fibre bundles and transfixing axons clearly stand out on the negative reaction of the nucleus of the descending trigeminal root (right). The peripheral fibres (left) show a weaker reaction than the descending trigeminal tract. Periodic-acid-Schiff × 80.

FIG. 4.—Genu of the facial nerve showing both transversally and longitudinally cut fibres exhibiting strong phosphorylase activity. Periodic-acid-Schiff × 80.

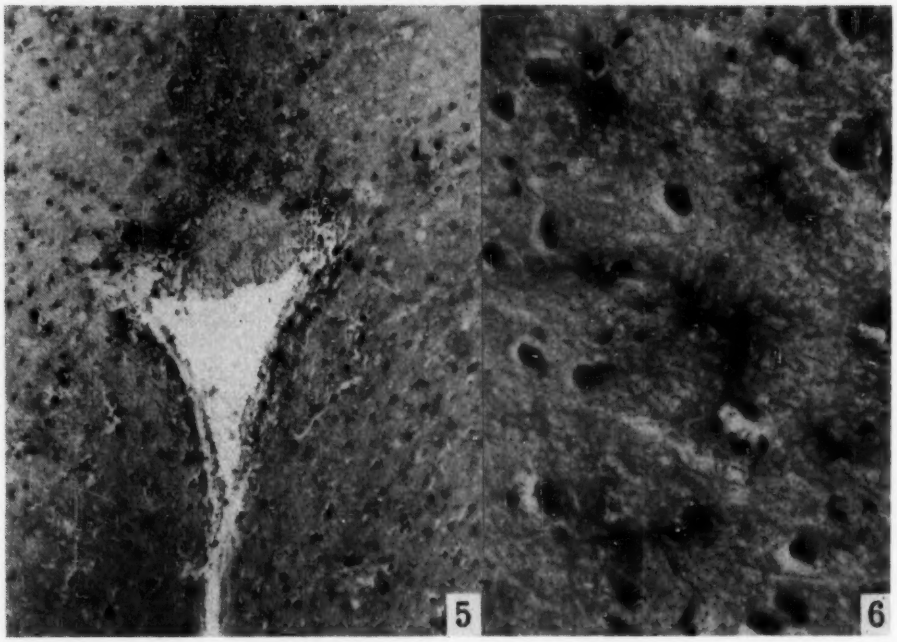

FIG. 5.—Oral portion of the aqueduct. The subcommissural organ and the ependyma show no reaction; a strong reaction is found in the subependymal glial tissue, and mild, diffuse reaction in the central gray matter. Periodic-acid-Schiff × 80.

FIG. 6.—Lateral part of the tuber cinereum showing phosphorylase activity in glial cells. A faint counterstaining by chromalum gallocyanin shows neurons without reaction. Periodic-acid-Schiff × 320.

frozen sections of fresh tissue, 60μ thick, prepared by the author's technique (Friede, 1958b). (This article may be consulted for further details.) Both "tetrazolpurpur", Bayer (4,4-bis 3,5-diphenyl-2-tetrazoliumbiphenyl) chloride (Neumann and Koch, 1953) and "nitro BT" (Nachlas, Tsou, De Souza, Cheng, and Seligman, 1957) were employed.

Strong phosphorylase activity and weak or no succinic dehydrogenase activity coincided in the white matter, the subependymal glial tissue, and the glial tissue of the raphe.

Weak phosphorylase activity and strong succinic dehydrogenase activity coincided in the ependymal cells and in neurons and neuropil of many of the brain's nuclei. Many other nuclei, however, showed mild or strong phosphorylase activity instead of their strong succinic dehydrogenase activity. In such nuclei an inverse relationship of the enzymes may nevertheless be present, since a loss of succinic dehydrogenase has been observed during the incubation for phosphorylase in portions of the specimens which were exposed to mechanical damage and exhibited strong phosphorylase reaction (Friede, 1959a).

An inverse relationship was not evident in glial tissue. Glial cells seem to contain none or weak succinic dehydrogenase activity. A consistent phosphorylase reaction, however, was found only in the glia of the periventricular gray matter and in the subependymal glia.

No inverse relationship was found in the subcommissural organ which lacked both phosphorylase and succinic dehydrogenase activity. Moreover, the nucleus of the tractus solitarius, the dorsal vagal nucleus, the locus caeruleus, and the pars compacta of the substantia nigra exhibit rather weak phosphorylase activity and none or weak succinic dehydrogenase activity (Shimizu and Morikawa, 1957).

An inverse relationship of the enzymes is lacking also in the developing rat's brain, which biochemically (Potter, Schneider, and Liebl, 1945) and histochemically (Friede, 1959b) exhibits weak succinic dehydrogenase activity but also shows biochemically (Shapiro and Wertheimer, 1943) and histochemically (Shimizu and Okada, 1957; Friede, 1958a) weak phosphorylase activity.

Discussion

Phosphorylase activity in white matter has been demonstrated histochemically in both fresh frozen tissue sections (Shimizu and Okada, 1957) and in hand-cut tissue specimens. In the latter, the localization of the enzyme activity was more detailed

than the diffuse reaction in sections; the gross distribution, though, was similar. The evaluation of the findings in gray matter, however, is most difficult. The reaction in tissue sections was reported as being highly labile (Shimizu and Okada, 1957). In tissue specimens, a strong reaction in gray matter seemed to depend on tissue damage during the preparation. Weak or no phosphorylase activity was found in most nuclei especially if any tissue damage was avoided, including cutting of sections. The weak or negative reaction of gray matter was not simulated by inadequate diffusion conditions within the tissue specimen since transfixing axons in the gray matter showed typical strong phosphorylase reaction. It does not seem likely that the reaction is weakened in gray matter by a competitive consumption of the glucose phosphate, since the glycolysis was blocked by iodoacetate, and since the reaction of the transfixing axons would be weakened as well.

A strong phosphorylase activity in neurons was found to be accompanied with artificial cell shrinkage (Friede, 1959a). The physiological phosphorylase activity of gray matter, therefore, seems rather low, but relatively slight tissue damage seems to activate the enzyme which may be present in an inactive stage. In the first 30 seconds of anoxia, as an example, glycolysis was reported increased to 10 times the aerobic glucose utilization (Opitz and Schneider, 1950).

It is not clear whether some regions of gray matter which consistently show phosphorylase activity (as the upper portions of the cerebral cortex or the molecular layer of the cerebellar cortex) are extremely sensitive to a preparative damage or physiologically if they exhibit enzyme activity. The very strong phosphorylase activity found in the habenula and the interpeduncular nucleus may bear a relationship to the outstanding activity of alkaline phosphatase in these nuclei (Shimizu, 1950).

The activation of phosphorylase by tissue damage may explain the much higher activity rates found in gray matter by biochemical techniques involving tissue destruction: in the cerebellum, phosphorylase activity of 2·79 units in the molecular layer, 2·76 units in the granular layer, and 1·62 units in the subjacent white matter was found (Robins, Smith, and Jen, 1957). These results are in contrast to the weak phosphorylase activity found in the granular layer by histochemical techniques. Sensitivity to tissue damage probably also explains why it is possible to obtain a cytochemical demonstration of an enzyme which has a very poor structural binding if investigated by biochemical techniques.

An inverse relationship of phosphorylase activity and succinic dehydrogenase activity is generally found, though exceptions are not rare. This inverse relationship may be considered indicative for different aerobic or anaerobic metabolic rates.

Summary

The histochemical distribution of phosphorylase activity in the brain of the guinea-pig is described with a technique providing an improved localization of the enzyme activity. Strong phosphorylase activity was found in axons in both white and gray matter. Rather weak activity was noted in the neuropil and neurons of gray matter. Even extremely slight tissue damage was found to alter the reaction. The histochemical distribution of phosphorylase activity and succinic dehydrogenase activity generally was inverse but a few exceptions were noted in particular regions.

REFERENCES

Bradfield, J. R. G. (1951). *Nature (Lond.)*, **167**, 40.
Dempsey, E. W., and Wislocki, G. B. (1944). *Endocrinology*, **35**, 409.
Friede, R. (1956). *Arch. Psychiat. Nervenkr.*, **195**, 325.
—— (1958a). *Hoppe-Seyl. Z. physiol. Chem.*, **310**, 4.
—— (1958b). *J. Histochem. Cytochem.*, **6**, 347.
—— (1959a). *Ibid.*, **7**, 34.
—— (1959b). *J. Neurochem.*, **4**, 101, 111.
Nachlas, M. M., Tsou, K. C., De Souza, E., Cheng, C. S., and Seligman, A. M. (1957). *J. Histochem. Cytochem.*, **5**, 420.
Neumann, K., and Koch, G. (1953). *Hoppe-Seyl. physiol. Chem.*, **295**, 35.
Opitz, E., and Schneider, M. (1950). *Ergebn. Physiol.*, **46**, 126.
Potter, V. R., Schneider, W. C., and Liebl, G. J. (1945). *Cancer Res.*, **5**, 21.
Robins, E., Smith, D. E., and Jen, M. K. (1957). In *Ultrastructure and Cellular Chemistry of Neural Tissue*, ed. H. Waelsch, p. 205. Hoeber-Harper, New York.
Shapiro, B., and Wertheimer, E. (1943). *Biochem. J.*, **37**, 397.
Shimizu, N. (1950). *J. comp. Neurol.*, **93**, 201.
——, and Morikawa, N. (1957). *J. Histochem. Cytochem.*, **5**, 334.
——, ——, and Ishi, T. (1957). *J. comp. Neurol.*, **108**, 1.
——, and Okada, M. (1957). *J. Histochem. Cytochem.*, **5**, 459.
Takeuchi, T., and Kuriaki, H. (1955). *Ibid.*, **3**, 153.

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CONGENITAL INTRAORBITAL ARTERIOVENOUS ANEURYSM

BY

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Aneurysms or malformations of the intraorbital vessels are lesions which in spite of the large number of cases cited in the medical literature have rarely been verified, the larger part being merely clinical descriptions.

In 1823, Guthrie described the first case of intraorbital aneurysm proved by post-mortem examination. Pulsating exophthalmos was the most striking feature of this case, and for many years after this description pulsating exophthalmos was thought to be pathognomonic of intraorbital aneurysm (Dempsey, 1886; Nunneley, 1859). In 1865 Nunneley extended the pathological possibilities by describing two cases of pulsating exophthalmos due to an aneurysm of the internal carotid in one case and to an intracranial extension of a thyroid carcinoma in the other.

In 1870, Delens reviewed the whole problem of pulsating exophthalmos and identified a carotid cavernous fistula as the most common cause, and from that time intraorbital aneurysms seem to have been almost forgotten. This can be seen in the publications of Locke (1924) and Martin and Mabon (1943) followed in 1920 by Sattler who referred to five supposed arteriovenous aneurysms, not verified, as a cause of pulsating exophthalmos.

In 1949, Heimburger, Oberhill, McGarry, and Bucy reviewed the published cases of intraorbital aneurysm and found that only in six was the lesion verified. After studying the descriptions given, they came to the conclusion that in many cases the ocular symptoms were probably due to carotico-cavernous fistulas or vascular lesions of endocranial origin. They added one case of their own of non-pulsating exophthalmos of the left eye of rapid development. It was accompanied by congestion, pain, conjunctival oedema, amblyopia, increase of ocular pressure, and dilatation of the veins of the retina, followed later by haemorrhages. This case was explored and a great dilatation of the lacrimal artery was found, without any evidence of other vascular abnormalities. Ligation of the enlarged artery was followed by recession of the clinical symptoms.

The following case presents a clinical picture of an intraorbital arteriovenous aneurysm, verified by angiography.

Case Report

E.C.F. (H.Cl., S.O.E.41.402), a woman, 31 years of age, was first seen on September 18, 1957. She stated that in the last two years, without any pathological antecedent or trauma, she noticed on bending the head a feeling of tension around the left eye. The various ophthalmologists who had seen her could not find any changes in the visual acuity, fields, or fundi.

During the last three months these troubles had increased, appearing with any forward inclination of the head. Two months previously she had suffered an acute episode accompanied by diplopia and transient amblyopia lasting half an hour. The diplopia coincided with periods of intense palpebral oedema. These crises passed on lifting the head. The patient did not complain of headache or subjective cranial bruit at any time.

Examination showed a normal young woman, bright and alert. The superficial venous network of the eyelids was perhaps more obvious than usual, especially on the left side. A mild exophthalmos was present on the same side, the protrusion being 6 mm. more than on the right side. With the head erect, the left palpebral fissure was slightly narrower than the right (Fig. 1A), and there was also mild conjunctival congestion. The pupils were equal and reacted normally. Pressure on the left jugular vein, or bending of the head, produced palpebral swelling and a slight increase of the left exophthalmos (Fig. 1B).

The visual acuity was 90/100 in the right eye, and 50/100 in the left eye. With proper correction for its myopic astigmatism, the visual acuity in both eyes rose to 100/100. Ocular motility was normal, but there was a mild intermittent imbalance of the muscular equilibrium, due to deviation of the left eye. The visual fields showed in the right eye a mild upper temporal depression. In the left eye there was a concentric reduction for white and colours and a depression in the upper nasal quadrant.

The fundi were normal except for a mild venous congestion on the left. Otherwise, the neurological and systemic examinations were normal. The blood pressure was 130/85 mm. Hg. No bruit was audible over the head or eyeballs.

No abnormalities were found in the *x*-ray examination of the head, including the orbits and the optic canals. Bilateral carotid angiography was carried out. No abnormalities were observed on the right side. On the

FIG. 1.—Palpebral fissures at rest (A) and during jugular compression (B).

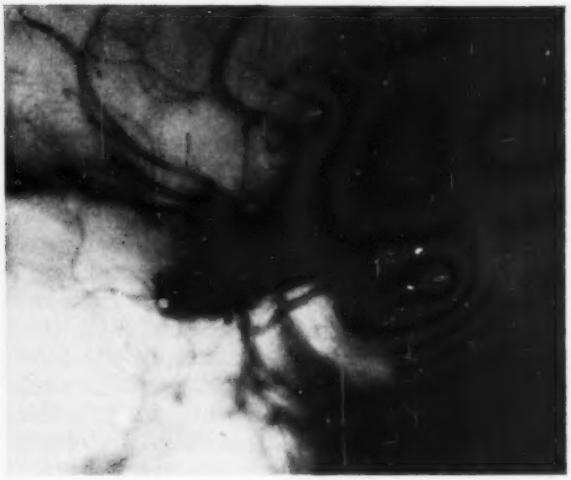

FIG. 2.—Carotid angiogram, lateral projection. Note arteriovenous aneurysm in posterior part of orbit.

FIG. 3.—Carotid angiogram, early (A) and late (B) stage in axial projection. Note arteriovenous aneurysm in upper part of orbit.

left a lesion was demonstrated in the postero-superior part of the orbit. Its appearance was typical of an arteriovenous aneurysm, of which the arterial supply probably came from the lacrimal artery, a branch of the intraorbital portion of the ophthalmic artery (Figs. 2 and 3). The venous drainage of the lesion was by way of the superior ophthalmic vein. No abnormality was seen in the intracranial vessels.

Discussion

This case demonstrates an intermittent exophthalmos. The first description of this type of exophthalmos was published by Schmidt in 1805, and although they are rare, in 1944 Walsh and Dandy collected 111 published reports of which the majority were merely clinical observations. The commonly accepted aetiology of intermittent exophthalmos (Cordero, 1935; Hippert, 1936; Olivella, 1946) is that of an orbital varicocele, caused according to Birch-Hirschfeld (1930), by a complete or partial blockage of the venous drainage of the orbit into the jugular vein. In 1944 Walsh and Dandy published one of their own cases of intermittent exophthalmos due to an extensive arteriovenous aneurysm situated within and behind the sphenoidal fissure and extending through the dura mater to the Gasserian ganglion and the cavernous sinus. The lesion was demonstrated at operation, and was the first case of verified aetiology. Later, Walsh (1947) published another case in which a great varicosity was found situated in the sphenoidal ridge. Senà in 1955 cites a series of published cases of known aetiology, namely, diffuse angioma, congenital vascular tumour, lymphosarcoma, ethmoiditis, pituitary tumour, cavernous angioma, etc. None of these cases was angiographically verified, but Huber (1951) published a case similar to our own in which the lesion was so verified.

Concerning the treatment, we must confess that we have no previous experience with intraorbital arteriovenous aneurysms. From our experience with similar intracranial lesions, we had the impression that the lesion in the present case could be removed surgically. However, we could not guarantee that in doing so there would not be the possibility of damaging the function of the optic or oculomotor nerves, either by direct injury or as a result of the surgical interference with the blood supply of the eye or the orbit. We discussed the matter with the patient, and as she had not had any pain yet and her visual function was so well preserved, she decided not to accept the risks of an operation at present unless new circumstances arose.

The authors wish to express their sincere thanks to Dr. F. Palomar for his ophthalmological cooperation.

Bibliography

Birch-Hirschfeld, A. (1930). In *Kurzes Handbuch der Ophthalmolgie*, vol. 3, ed. F. Schieck and A. Brückner. Julius Springer, Berlin.
Cordero, C. (1935). *Arch. Otal.*, **42**, 18.
Delens, E. (1870). "*De la communication de la carotide interne et du sinus caverneux (anévrysme artério-veineux)*". Adrien Delahaye, Paris. Thèse.
Dempsey, A. (1886). *Brit. med. J.*, **2**, 541.
Guthrie, G. J. (1823). Aneurysms within the orbit. *Lectures on the operative surgery of the eye*. Burgess and Hill, London.
Heimburger, R. F., Oberhill, H. R., McGarry, H. I., and Bucy, P. C. (1949). *Arch. Ophthal., (Chicago)*, **42**, 1.
Hippert, F. (1936). *Arch. Ophtal. (Paris)*, **53**, 135.
Huber, A. (1951). *Bull. Mem. Soc. franç. Ophtal.*, **64**, 347.
Locke, C. E., Jr. (1924). *Ann. Surg.*, **80**, 1 and 272.
Martin, J. D. Jr., and Mabon, R. F. (1943). *J. Amer. med. Ass.*, **121**, 330.
Nunneley, T. (1859). *Med.-Chir-Trans. London*, **42**, 165.
—— (1865). *Ibid.*, **48**, 15.
Olivella, A. (1946). *Arch. Soc. oftal. hisp.-amer.*, **6**, 905.
Sattler, C. H. (1920). Pulsierender exophthalmus. In *Handbuch der gesamten Augenheilkunde*, 2nd ed., ed. A. Graefe and T. Saemisch, band 9, abt. 1, teil 2. Springer, Berlin.
Schmidt (1805). Cited by Senà, J. A.
Senà, J. A. (1955). *Sem. méd. (B. Aires)*, **106**, 805.
Walsh, F. B. (1947). *Clinical Neuro-ophthalmology*, pp. 846-850. Williams and Wilkins, Baltimore.
——, and Dandy, W. E. (1944). *Arch. Ophthal. (Chicago)*, **32**, 1.

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NEUROLOGICAL CHANGES WITH INTRACAROTID AMYTAL AND MEGIMIDE IN MAN*

BY

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Alterations in cerebral function produced by intravenously administered drugs are well known. Of these, two classes of drugs are of particular interest in diagnostic neurology: barbiturate and analeptic substances. These drugs have been used to elicit changes in function and neurological defects not otherwise apparent and to help to localize cerebral pathology.

The use of drugs, especially "metrazol" (pentamethylenetetrazol), to produce seizures, often focal in the presence of lateralized cerebral pathology, is well documented (Ajmone-Marsan and Ralston, 1957). The pharmacology of the convulsant agents at the synapse may vary greatly but the behavioural effects produced by intravenous administration are phenotypically alike. For example, "metrazol" is an activator of excitatory synapses (Purpura and Grundfest, 1957) while "megimide" (B-B ethyl, methyl glutarimide) is a mild activator of excitatory synapses which exerts its greatest action as a blockader of inhibitory synapses (Purpura, 1958). Despite these differences, both drugs produce similar seizures in the same patient. Patterned focal modes of onset of intravenously produced "metrazol" seizures, with the exceptions of lateralized non-adversive arm jerks and head and eye deviation, localize areas of cerebral dysfunction (Ajmone-Marsan and Ralston, 1957).

Amytal (sodium amobarbital) has been used most widely among the barbiturates in diagnostic neurology. Amytal has been used in eliciting latent organic psychoses (Weinstein, Kahn, Sugarman, and Linn, 1953), sensory defects (Bender and Nathanson, 1950; Jaffe, 1957), and motor deficits (Teng and Bender, 1955). Patients without cerebral disease respond to intravenous "amytal" with nystagmus, dysarthria, ataxia, and sleepiness. The evoked, lateralized findings in neurological patients are always seen against a background of these responses.

While there have been many reports on the effects of the intravenous use of these drugs, behavioural observations with arterial instillation have been rare. Bennett (1953) injected "metrazol" into the carotid and vertebral arteries of patients with petit mal, producing petit mal states in unanaesthetized patients. Wada (quoted by Roberts, 1958a and b) has used "amytal" and Kjellberg (1959) has used "nembutal" (sodium pentobarbital) in studies on the mechanisms of aphasia produced by carotid injection. These observers find that injection of one side produces aphasia, and injection of the other side does not. Jarvik and Rothballer (1958) reported contralateral circling in cats with "amytal" injected into the carotid, and noted the marked differences between feline and primate carotid artery distributions.

The use of drug injections into the carotid artery permits one to study the pharmacology of a portion of the brain that is relatively restricted by the arterial circulation pattern. Comparison of the results of intravenous and intracarotid injections of a drug should help in localizing the sites of action of the drugs used. However, one must bear in mind the time necessary for circulation to the uninjected hemisphere and basilar system, a period of less than 20 seconds. Observations made before recirculation has occurred are of necessity qualitatively different from those made after recirculation of the drug. With this limitation in mind, the present study was undertaken.

Material

Seventeen studies were carried out in 16 patients ranging in age from 17 to 81 years. The patients were undergoing carotid arteriography for a variety of neurological conditions including seizure disorders, migraine, cerebral neoplasms, subarachnoid haemorrhage, post-encephalitic Parkinsonism, and cerebrovascular disorders.

Method

The patients were all studied after arteriography using "hypaque", when the placing of the needle and circulation patterns could be verified. All

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patients showed filling of the cerebral circulation confined to the ipsilateral hemisphere as far as could be determined by arteriography. The Cournand arterial needle was used to allow for stability of the position of the needle and to minimize discomfort to the patient. Either no premedication or small amounts of atropine were given, The drugs, diluted with normal saline, were rapidly injected in 0·5 to 2·0 ml. volumes.

Throughout the procedure the patients were examined by two or more neurologists. At times motion pictures were taken that were subsequently analyzed to confirm behavioural observations. Electroencephalograms (E.E.G.) were recorded throughout on an eight-channel ink-writing electroencephalograph. Communication was evaluated by these tests, namely, naming of objects, counting, comprehension, and spontaneous speech.

Preliminary and control observations were made with saline, "hypaque", "diodrast", atropine, "tensilon", ethanol, "decholin", caffeine, and histamine. No E.E.G. changes were noted with these drugs. Minor and inconsistent behavioural changes were seen including headache (histamine), sleepiness and diffuse paraesthesiae (ethanol), tone changes ("tensilon", atropine), unpleasant taste ("decholin"), and increased pulse rate (atropine). Megimide and "amytal" were administered after these observations. Fourteen of the patients were also studied with intravenous amytal on separate occasions.

Results

Electro-encephalographic and behavioural changes resulted in all cases after "megimide" and "amytal" injected into the carotid artery. The E.E.G. changes were invariably high-voltage, bilateral slow bursts, at times accompanied by spikes and at times accentuated on the injected side. The E.E.G. changes are reported in detail elsewhere (Werman, Christoff, and Anderson, 1959b). The behavioural effects are the subject of this paper and have already been presented in preliminary form (Werman *et al.*, 1959a).

Megimide.—All patients responded to adequate doses of "megimide" injected into the carotid with motor seizures. The range of effective dosage was surprisingly narrow: all patients responded to 20 mg., with a minimal effective dose of 10 mg. The average intravenous dose to produce seizures in another and much larger group of patients was between 300 and 400 mg. (unpublished observations, this laboratory). The ratio of the greatest to the least minimum effective seizure dose by the carotid route is 2:1 compared with an intravenous ratio of greater than 15:1.

All seizures began focally and showed deviation of the head with or without accompanying movement of the eyes away from the injected side. There was always at least one initial movement of the contralateral arm. Less frequently, twitching of the contralateral face was seen. An adversive onset was seen in one patient. Most of the seizures progressed and became generalized, although they were usually observed to be more violent contralaterally.

None of the patients exhibited unusual seizure patterns. The movements were mostly tonic-clonic, less often somewhat myoclonic. The seizures lasted from 15 seconds to two minutes and all began within five seconds of injection. One seizure remained focal for 45 seconds and never became generalized.

One patient, a woman with grand mal seizures and a left occipital slow-wave E.E.G. focus, was studied on two occasions. Megimide and "amytal" were injected into the left carotid artery during the first procedure and into the right carotid artery the second time. She exhibited mirror image seizures with threshold "megimide" dosage. After the injection of 10 mg. "megimide" into the left carotid artery there was a sudden violent jerk of the head to the right. After an appreciable latency, the eyes deviated from the mid-position to the right. First the right arm was extended, then the left. A generalized seizure ensued with apnoea, cyanosis, and clonic movements of all extremities lasting 90 seconds and followed by sleep. Injection of 10 mg. "megimide" into the right carotid artery produced a head jerk, deviation of the head to the left with the eyes remaining in mid-position, and a shrill scream. This was followed by extension of the left arm, then the right, generalized clonic movements, apnoea and cyanosis lasting 100 seconds and followed by sleep.

Amytal.—Amytal, 25 to 75 mg. injected into the carotid artery, produced behavioural changes in all patients when rapidly injected in 0·5 to 2·0 ml. volumes. On several occasions, patients received more than one injection. If separated by sufficient intervals, the results were regularly reproducible. Contralateral hemimotor defects were produced in all patients studied and were always the most striking and profound changes produced. Motor defects always appeared within five seconds and lasted from two to seven minutes and were at all times the last lateralized symptoms to disappear as the patient recovered. The hemiparesis was usually most marked in the arm, the face and leg each decrementally involved. One patient exhibited weakness most marked in the leg after "amytal" injected into the carotid artery of an apparently normal hemisphere. Of the 12 patients without Babinski toe

signs before intracarotid injection of "amytal", nine developed a contralateral Babinski sign and one developed bilateral Babinski signs. No ocular gaze palsies were observed.

All patients studied were right handed. There were five right carotid injections and 12 left-sided injections. Four of the patients with left carotid injections exhibited mild to moderate aphasic symptoms before injection, none of the right-sided group being aphasic. Following intracarotid injection of "amytal" there was no definite aphasia observed in the non-aphasic patients and no increase in communicative difficulties in the four aphasic subjects. Brief aphonia lasting less than 10 seconds was noted in three non-aphasic patients, two after left carotid injections and one after a right carotid injection. Dysarthria was found in five patients, appearing within 15 seconds in only one. This dysphasic patient was clearly dysarthric within five seconds after the intracarotid injection of "amytal". However, naming of objects, comprehension, and word usage were unaffected. Organic mental changes were not observed in any of the patients after intracarotid injection of "amytal".

The examination routine was directed at the most complete evaluation of language function and motor status possible within 15 seconds. Therefore sensory and field examinations were less complete. Moreover, those patients with sensory or field defects manifested these deficits for periods of less than two minutes. Adequate sensory testing was possible in nine patients, five of whom developed mild to moderate contralateral hemisensory defects, most easily elicitable on double simultaneous stimulation. Visual fields were adequately tested in eight patients, three developing contralateral homonymous hemianopias of moderate degree. The three patients with field defects also had sensory changes.

Nystagmus not present before intracarotid injection of "amytal" appeared in four patients receiving larger amounts of the drug and only after a latency of at least 20 seconds. All but two of the 16 patients studied were examined with intravenous "amytal" administered in increments until sleepiness was reported. Under these conditions, all patients developed nystagmus and dysarthria but in only three were lateralizing signs elicited. In these patients the increase in lateralizing findings was mild and far less dramatic than they exhibited with intracarotid "amytal".

The patient studied bilaterally had no neurological deficit on control examinations and intravenous "amytal" failed to produce lateralizing signs. Injection of 50 mg. "amytal" into the left carotid artery produced a mild right hemiparesis with Babinski sign, right-sided extinction and position sense errors, all appearing within five seconds. Neither aphasia nor a field defect could be elicited. The defects could no longer be obtained seven minutes after injection. Injection of 50 mg. "amytal" into the right carotid artery was followed within five seconds by a moderate left hemiparesis, a left homonymous hemianopia to double simultaneous stimulation, and poor point localization confined to the left side. There was no aphasia elicitable and all signs cleared in five minutes.

Comment and Discussion

Our results demonstrate that the effects of "megimide" and "amytal" injected into the carotid artery are different from those found with intravenous injection of these drugs. Although the subjects used displayed a variety of cerebral disorders, the patterns of contralateral onset of seizures with "megimide" and contralateral neurological deficits with "amytal" seemed to be independent of the underlying pathology. Moreover, the one patient studied bilaterally on separate occasions showed profound mirror-image congruence of effects to each of the drugs. The brief latencies and the angiographic check of unilaterality both speak for an ipsilateral hemispheric site of action for these drugs, as do the contralateral behavioural changes. Such variability as is reported can, to a large extent, be explained by nuances in cerebral circulatory patterns from patient to patient.

The lateralized behavioural responses to "amytal" and "megimide" injected into the carotid artery are singular and not reproduced by these drugs injected intravenously. The rapid injection of either drug into the carotid circulation acts on functional groupings in the cerebrum ordinarily not most sensitive to these drugs. The nystagmus, ataxia, dysarthria, and sleepiness seen with intravenous "amytal" are suggestive of brain-stem dysfunction. These responses are not seen with intracarotid administration unless larger doses of "amytal" are used and sufficient time has elapsed for recirculation to the uninjected hemisphere and posterior circulation.

The problem of localization of behavioural activity of a drug such as "amytal" is made difficult by the complex interrelations and functionally overlapping systems of the brain. One must keep in mind the now commonplace observation that in the presence of most lesions of the brain one observes behavioural defects caused not by the lesion but by the reorganization of the intact brain. For example, in the case of "amytal", intravenous administration will eliminate nystagmus present on direct forward gaze and thereby improve visual acuity (Bender, 1946; Nathanson, Bergman, and Bender, 1953).

This action is surprising in view of the fact that "amytal" consistently produces nystagmus on lateral gaze in normals. In these instances the mechanism is presumably that of two counterbalancing susceptible systems, a lesion of one leading to nystagmus, but both depressed by "amytal".

Our data do not contravert the possible brain-stem site of action of intravenous "amytal". Comparing the effects of bilateral simultaneous carotid injections of the barbiturate with those of vertebral injections would be a further aid in determining the threshold sites of action of the drug. These tests would help to discriminate between brain-stem effects and the strong possibility of a complex and diffuse response to intravenous "amytal".

Localization of the sites of action of intravenous "megimide" is even less clear than that for "amytal". The myoclonic jerks and grand mal seizures seen with intravenous "megimide" in patients without focal cerebral disease cannot be localized. It is of interest that the focal behavioural signs which are considered of least value in lateralization with intravenous "metrazol" (Ajmone-Marsan and Ralston, 1957) and probably with intravenous "megimide", *viz.*, non-adversive unilateral arm movements and head and eye deviations, are the very effects that are consistently contralateral with intracarotid "megimide". With intravenous analeptics the onsets of such seizures tend to be unrelated to the localization of pathology, and may vary from side to side in the same patient at different times. No ready explanation for this difference is apparent to us at present.

Bennett (1953) injected "metrazol" both into the carotid arteries and into the vertebral arteries of patients with petit mal seizures. With intracarotid "metrazol" petit mal states always followed but contralateral seizures were seen as well. With vertebral injections, petit mal states were rare and "although long grand mal discharges were frequently elicited, no clonic movements were ever observed". His conclusions on the mechanisms of petit mal disorders are subject to criticism because of (1) the restricted use of petit mal patients, and (2) the technique of repeating increasing doses of "metrazol" until the seizure threshold is reached. Repeated injections during one experiment allow for wide distribution of the drug throughout the brain. Bennett's findings, however, are provocative, suggesting a diffuse or bilateral origin of petit mal, and should be extended in the light of our results.

The success of Wada (quoted by Roberts, 1958a and b) and Kjellberg (1959) in producing aphasia with barbiturates injected into the carotid artery is not supported by our findings, The absence of disturbance in language or ability to communicate in our series was unequivocal in the periods both before and after one circulation time had elapsed even though all patients developed contralateral neurological defects. It should be noted that intravenous "amytal" has been reported to improve aphasia (Linn and Stein, 1946) but a more detailed study by Bergman and Green (1951) found that intravenous "amytal" had almost no effect on aphasia, increasing the deficit in an occasional patient.

Weinstein *et al.* (1953) demonstrated that a large percentage of patients with cerebral disorders develop organic mental syndromes with intravenous "amytal". Weinstein and Kahn (1952) further bring to our attention the language disturbance they call "nonaphasic misnaming" (paraphasia). This disturbance of communication, which superficially resembles aphasia, is not lateralizing and is seen only with bilateral cerebral disease and/or diencephalic lesions. Moreover, it is always accompanied by other manifestations of organic psychosis, including those produced by intravenous "amytal". This defect is characterized by misnaming of objects, persons, or places in terms of certain aspects of their function or structure, without other stigmata of aphasia. Roberts (1958b) reports a protocol of an intracarotid "amytal" injection by Wada's technique wherein the patient inititally becomes confused and then develops a "dysphasia", which is not further characterized.

The techniques used by Wada and Kjellberg in eliciting aphasia are different in important details from those used in the present study. Wada (Roberts, 1958b) injects "amytal" in dosages of 175 to 200 mg. more than twice the largest dose found necessary in our study to produce easily recognizable neurological symptoms. These large doses are comparable to the dosages of intravenous "amytal" necessary to elicit organic psychosis and other neurological defects in the most sensitive patients. Kjellberg (1959), using "nembutal", instils the drug by slow continuous infusion. In neither study are we told of any precaution to observe the patients before sufficient time has elapsed to distribute the barbiturate via the circulation throughout the brain. Also not indicated is the presence or absence of nystagmus, dysarthria, or other clinical evidence of generalized circulatory dispersion of the barbiturate.

The reported finding by both Wada and Kjellberg that aphasia is produced by their techniques on injection of one side and not the other is an important one. According to the views of Weinstein and Kahn (1955), intracarotid injection of barbiturate, acting on a normal hemisphere, could produce bilateral cerebral dysfunction in the patient whose other (uninjected) hemisphere contains a lesion, thereby causing an organic psychosis and accompanying communicative difficulties. However, this inter-

pretation does not hold when injection of the diseased hemisphere is the only side to produce aphasia. In such a case, one would like to know if both anterior cerebral arteries are not filled from the same side, a not uncommon situation.

Two further explanations for the discrepancies in the findings on aphasia are available. (1) The threshold for aphasia from barbiturate injected into the carotid artery is considerably higher than thresholds for other lateralizing hemispheric symptoms, and/or (2) aphasia can only be produced by intracarotid barbiturate in the presence of smaller amounts of barbiturates throughout the brain. These interpretations are subject to confirmation by observing (1) the responses to larger doses of barbiturates before one circulation time has elapsed, and (2) the effects of smaller doses in patients premedicated by some other route.

The universal indication for carotid arteriography in the patients used in this study resulted in a highly selected group. However, the diversity of the pathology exhibited and the independence of our results from the underlying disease would partially mitigate the defect of such limited sampling. The diagnostic value of intravenous "amytal" and "megimide" does not appear to be significant. However, the usefulness of intracarotid drug research is attested to by the implications for future study of cerebral physiology and pharmacology.

No serious or persistent morbidity was noted in our study. We feel that judicious administration of intracarotid drugs in humans is a safe procedure and a valuable research method.

Summary

The behavioural changes after the rapid intracarotid injection of "amytal" and "megimide" are reported. A distinction is drawn between those findings occurring before and those after sufficient time has elapsed to allow recirculation to other parts of the brain.

Seventeen studies on 16 patients are reported, one patient receiving bilateral injections on separate occasions. Although the patients displayed a variety of cerebral lesions, the results were strikingly independent of the location and nature of the disease.

Megimide induced motor seizures most marked contralaterally, with universally contralateral onset.

Amytal produced contralateral motor, sensory, and visual field defects. At no time was aphasia seen. The finding of aphasia by other workers using intracarotid drugs in humans is a safe procedure; effects of the drug are essentially those found with intravenous "amytal".

The sites of action of "megimide" and "amytal" are discussed.

We should like to express our appreciation to Dr. Morris B. Bender, whose advice and encouragement made this study possible.

Addendum

Since this paper was submitted, a book has appeared with further discussion of the Wada technique (Penfield and Roberts, 1959). On page 98, we find the following pertinent comment on their results: "The sodium amytal aphasia test . . . has not given clear-cut evidence of bilateral representation of speech but has shown some equivocal results." This statement gains added meaning in the light of our results and discussion.

References

Ajmone-Marsan, C., and Ralston, B. L. (1957). *The Epileptic Seizure*. Charles C. Thomas, Springfield, Ill.
Bender, M. B. (1946). *Confin. neurol. (Basel)*, **7**, 144.
——, and Nathanson, M. (1950). *Arch. Neurol. Psychiat. (Chicago)*, **64**, 501.
Bennett, F. E. (1953). *Neurology*, **3**, 668.
Bergman, P. S., and Green, M. (1951). *Neurology*, **1**, 471.
Jaffe, R. (1957). *Ibid.*, **7**, 531.
Jarvik, M. E., and Rothballer, A. B. (1958). *Proc. Amer. Acad. Neurol.*, **10**, 56.
Kjellberg, R. N. (1959). *Trans. Amer. Neurol. Ass.*, 1958, p. 76.
Linn, L., and Stein, M. H. (1946). *Bull. U.S. Army med. Dept.*, **5**, 705.
Nathanson, M., Bergman, P. S., and Bender, M. B. (1953). *A.M.A. Arch. Neurol. Psychiat.*, **69**, 427.
Penfield, W., and Roberts, L. (1959). *Speech and Brain Mechanisms*. Princeton University Press, Princeton, N.J.
Purpura, D. P. (1958). Personal communication.
——, and Grundfest, H. (1957). *J. Neurophysiol.*, **20**, 494.
Roberts, H. L. (1958a). *Res. Publ. Ass. nerv. ment. Dis.*, **36**, 449.
—— (1958b). *A.M.A. Arch. Neurol. Psychiat.*, **79**, 275.
Teng, P., and Bender, M. B. (1955). *Neurology*, **5**, 777.
Weinstein, E. A., and Kahn, R. L. (1952). *A.M.A. Arch. Neurol. Psychiat.*, **67**, 72.
——, —— (1955). *Denial of Illness*. Charles C. Thomas, Springfield, Ill.
—— ——, Sugarman, L. A., and Linn, L. (1953). *Amer. J. Psychiat.*, **109**, 889.
Werman, R., Anderson, P. J., and Christoff, N. (1959a). *Electroenceph. clin. Neurophysiol.*, **11**, 267.
——, Christoff, N., and Anderson, P. J. (1959b). *Trans. Amer. Neurol. Ass.*, 1958, 83rd ann. meeting, p. 74.

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THE PROGNOSIS FOR AFFECTIVE ILLNESS WITH OVERT ANXIETY

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Not the least of our problems in psychiatry is the ubiquitous anxiety state. These patients are an unsatisfactory group because there seem to be no established indications for treatment, and it is rare to find anyone who is prepared to give an unequivocal prognosis. This is due in large measure to the fact that anxiety is a word having varying connotations, so that "anxiety state" is not a precise term. Even if anxiety is strictly defined there are still a number of different conditions having this symptom in common, and which may all therefore be reasonably called anxiety states. For this reason questions about the treatment of anxiety states have little real meaning, and it is easy to see how such methods as individual psychotherapy, group therapy, tranquillizers, modified insulin, and even electroconvulsive therapy, may all be mentioned at some time during the course of a discussion on this subject. Until we have a working classification and some agreement about the untreated prognosis for these illnesses, there can never be unanimity about the indications for treatment, or any useful evaluation of the treatments.

This article is concerned with the classification of illness confidently diagnosed as affective (as opposed to schizophrenic or organic), and in which anxiety is the cardinal presenting symptom. Illness in which anxiety was incidental, but not predominant, has been excluded. It is probably because of this that patients, with one exception, are from the age group 20 to 35 years.

It is imperative to be clear about the boundaries of the subject under investigation, and "anxiety" in this context refers to manifest, overt, or free-floating anxiety. This is variously described by the patient as a feeling of fear, panic, tension, or, more descriptively, as a sensation of being wrought up, or of expecting something unpleasant to happen. Physiological concomitants of fear are almost invariably present. Common ones are described as palpitations, rapid heart beats, missed heart beats, or a sudden empty feeling in the pit of the stomach. The less common are complaints of diarrhoea, frequency of micturition, and a sudden sensation of dizziness or instability. The fear may be nameless, or secondary elaboration may occur so that anxiety becomes centred, for instance, on the idea of heart disease or death. Bodily symptoms may occasionally be the first or main complaint, but the feeling of acute anxiety is always present.

This definition of anxiety excludes from the study all those anxiety states, anxiety hysterias, or organ neuroses in which somatic symptoms are unaccompanied by manifest anxiety or tension.

All the patients considered were under my care and supervision from the onset of their illness. They were selected from among consecutive outpatients using the criteria listed below, and were seen in departments serving rural, urban, and metropolitan-suburban districts of Surrey and Sussex. Throughout the study the treatment was not definitive, and consisted of varying admixtures of superficial reassurance and amylo-barbitone, grain ¾. It can reasonably be described as expectant.

The fundamental basis of classification was prognostic. In addition, it seemed to me that other reasonably objective criteria having possible predictive value could be set up based on the mode of onset, and the method of progression or course of the illness.

Presenting symptoms were used for classification; some patients changed their symptoms as time passed, but they were not reclassified.

The criteria are as follows :—

Prognostic Criteria

Group 1.—Patients show complete recovery without residual symptoms. Follow-up after recovery was not less than three months.

Group 2.—Patients fail to recover. The minimum period of continuous illness for inclusion in this group was two years.

Group 3.—Patients show partial recovery, or relapse rapidly after apparent recovery. The whole

of this group was arrived at by a process of exclusion from Groups 1 and 2, and not by positive selection.

Patients were not included in Group 2 until they had been ill continuously and without remission for two years.

Mode of Onset

Instantaneous.—This is to be interpreted literally. The illness begins suddenly, and without warning, and is then fully established.

Rapid.—The illness builds up over a matter of hours, or a few days at the most. If the process involves days there may be some fluctuation in the intensity of the upward trend of the symptoms.

Gradual.—Symptoms increase in frequency and severity over a period of weeks or months until a constant level is attained. Frequency as well as severity is included, so that the group includes a common type in which the presenting attack may be instantaneous, but recurrences are initially sporadic and only gradually increase in frequency until a pattern is established.

Progression or Course

Episodic without Precipitation.—The illness occurred in discrete bouts with a well-defined onset and termination, and in the interval the patient was normal, or at least his state was in no way comparable with that during attacks. There was no apparent cause for the attacks.

Episodic with Precipitation.—In this group attacks were related, for instance, to the necessity to go out or to meet people. The patient was well between attacks.

Constant but with Unprecipitated Exacerbation.—The patients here experienced a constant state of anxiety with episodic increases in tension for no apparent reason.

Fluctuating.—This is certainly a heterogeneous group. The first general characteristic was a more or less constant level of tension which lacked the sustained intensity of that in the group "constant but with unprecipitated exacerbation". The tension abated completely at times in some individuals. It seemed to be a constitutional defect rather than an acquired symptom. Superimposed were exacerbations of tension, usually on having to perform incidental or routine acts which would constitute a minimal stress for the average individual.

One group of patients was excluded from the study despite the fact that they showed anxiety as a major symptom. These were those with phobic states. They were excluded because they are already identifiable clinically as a group, and are, therefore, able to be classified (Mayer-Gross, Slater, and Roth, 1954). This is not to imply that they do not merit investigation on other accounts, or, in particular, that the prognosis for this illness is well established. Patients excluded had to conform with the following description. They showed anxiety as a major symptom, and they experienced this in a particular setting, or by contemplation that this situation might arise. The cause of the anxiety lay in the specific fear of what might happen in the particular situation. The fear was recognized by the patient as irrational, and was resented, but without influencing the anxiety. These phobic states are to be distinguished from superficially similar states in which free-floating anxiety gradually becomes fixed to one or more situations. The latter syndrome was included in the study. It is less well defined, and has more variants than the phobic states. Because the anxiety becomes centred, for instance, on crowds or queues, the illness may be designated as a specific phobia, *e.g.*, agarophobia, or a phobic anxiety state, and there is frequently no attempt made at differentiation from the phobic states. In practice, phobic state, phobic anxiety state, and phobia tend to be used indiscriminately. Examples may serve to underline differences.

The patient with a phobic state may be unwilling to go to the cinema because of the intrusive idea that the gallery will fall and kill her. This idea is resented and resisted, but the patient remains intensely anxious so long as she is in the cinema.

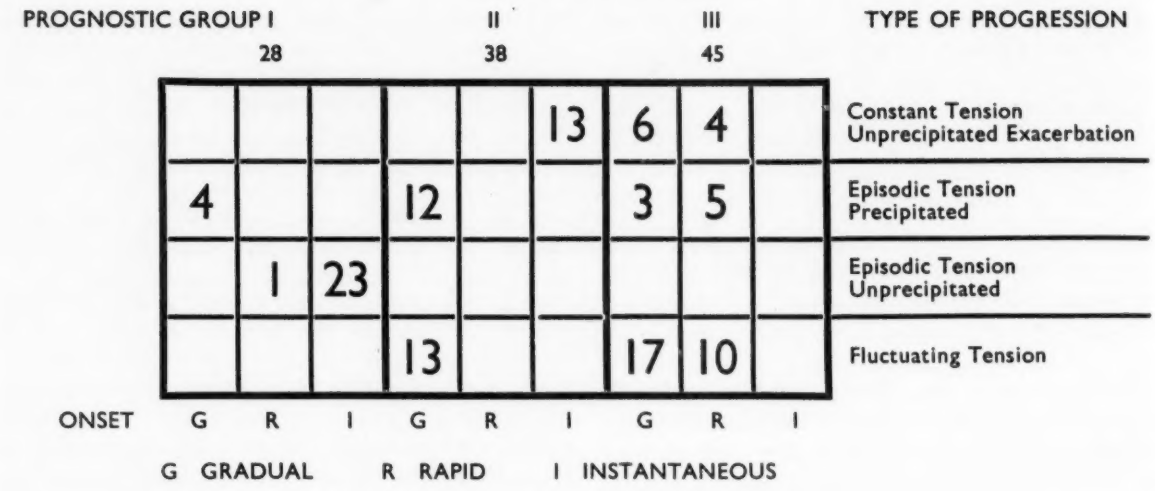
The patient with a phobic anxiety state experiences anxiety symptoms, and comes to fear going out in case she has an incapacitating attack in public. The attacks are infrequent at home, but increase in frequency and severity the further the patient goes from home. There is no compulsive element involved here, and the patient does not resist or resent the thought which keeps her at home, because it is the logical sequel to the anxiety attacks which are the primary symptom.

Results

The classification of 111 patients is shown in Fig. 1. Tests show that in form of onset and ultimate prognosis the episodic without precipitation group is highly significantly different from the others.

Discussion

This is a clinical study having as its objective the classification of patients with overt anxiety. The criteria were chosen because they were reasonably objective, and because I hoped they might have predictive value. The results establish significant



					13	6	4		Constant Tension Unprecipitated Exacerbation
4			12			3	5		Episodic Tension Precipitated
	1	23							Episodic Tension Unprecipitated
			13			17	10		Fluctuating Tension
ONSET	G	R	I	G	R	I	G	R	I

G GRADUAL R RAPID I INSTANTANEOUS

FIG. 1.—Classification of 111 patients with anxiety symptoms.

relationships, but, with one exception, it is not possible to make out a case for the delineation of clinical syndromes. The exception is that group of patients described as "episodic without precipitation" and for whom the onset of the illness is almost always instantaneous and the outcome invariably good.

The following is a description of a typical case :—

The onset of acute anxiety is instantaneous, unrelated to circumstances at the time, and comes as a complete surprise to the patient. There may be associated somatic symptoms other than those of pure anxiety, for instance, odd paraesthesiae. The anxiety attacks are episodic, of an order of frequency of two per day, tending to maintain a schedule with individual patients. The episodes are sudden in onset, but die away more gradually. Between attacks the patient is relatively normal, although tending to be irritable or morose. Throughout the illness the patient resists the onset of attacks, and indulges in furious self-recriminations because of his or her inability to prevent them. Patients become voluble on this point so that I have seen them regarded as hysterical.

Commonly the patients have vague, ill-formulated, gloomy forebodings, and become reluctant to plan, and are increasingly inert. This gloomy feeling may be associated with intrusive thoughts that they have organic diseases, which they resist and regard as futile, but which they cannot quite dismiss. One patient said, "My wife wants new curtains, and we have got all the patterns, but now I cannot take an interest, because somehow I feel I shall not live to see them. I know this is silly, and I could kick myself". Depression as such is rarely a specific complaint.

Sleep and appetite are variable, and of little assistance in diagnosis. Weight is lost, but rarely more than a stone.

Previous attacks, all of them self limiting, had occurred in five of my cases, although almost all had had transient attacks in which episodes had occurred daily for up to 10 days, but the patient had not been to a doctor.

Personality was independent and energetic.

I find the episodic without precipitation type of illness consistently diagnosed and accepted as an anxiety state, whereas I believe the better diagnosis to be depression with episodic anxiety. The anxiety symptoms are so prominent that depressive symptoms may fail to be elicited, or the clinician may be misled into confusing symptoms with illness as is frequently the case when the word hysterical is used.

Briefly, the reasons for regarding the illness as depressive are as follows :—

Anxiety may be a symptom of depression (Lange, 1928 ; Lewis, 1934). Depressives get well (Ross, 1923). There is a well-defined onset resulting in a change of behaviour (Lange, 1928). The onset is in the third and fourth decades (Slater, 1938). Previous attacks are not uncommon (Rennie, 1939, 1942) and will be higher if the transient attacks are included. In addition, gloomy foreboding, self-reproach, and obsessional thinking, although not perhaps obtrusive, are frequently present.

Although the remaining 87 cases do not fall so readily into clinically recognizable groups, it is still possible to apply the results usefully to clinical problems. This can be done entirely objectively without making a formal diagnosis. For instance, where anxiety is of instantaneous onset, it can be

seen from Fig. 1 that patients fall into two groups, and the prognosis is good or bad, but never indifferent. The distinction between the alternatives may be made by deciding whether the patient is constantly tense or relatively normal between episodes.

Alternatively, clinical description may be invoked, and after a diagnosis has been formulated, the place of the patient in Fig. 1 may be assigned by applying the criteria of onset and course. If this is done it will be found that patients with undifferentiated tension states (Curran and Partridge, 1952; Pippard, 1955) fall mainly into the group "constant but with unprecipitated exacerbation". For these patients the outlook is never good and whether it is bad or indifferent seems to depend on the type of onset. Other chronic and undifferentiated tension states fall into the group "fluctuating". The patients I have called phobic anxiety states fall mainly into the group "episodic with precipitation". Patients who, in practice are loosely called recurrent anxiety states or merely neurotics, appear in the group "fluctuating". Having assigned a patient to a place in this table it is then possible to make inferences about the prognosis.

One type of patient who upsets an attempt at classification such as this is the transitional case which changes type from time to time. Some of these are true hysterics in whom tension is as much a conversion symptom as paralysis. In other instances it seems that affective illness must be an interacting system in which consistent patterns of reaction are the rule but in which not infrequently one type may be diverted as it were to a different set of circuits. It is noteworthy that in only about a quarter of my cases was this circuit spontaneously reversible. That is, spontaneous recovery was restricted to about 25% of the cases, and these were almost all those of the depressive type.

Summary

Patients presenting themselves with overt anxiety as defined have been classified using outcome as the primary criterion. Two subsidiary sets of criteria relating to onset and course use time relationship as their main basis for selection.

Significant inter-relationships are established, and the existence of one group is claimed as a discrete clinical entity probably best described as falling in the depressive section of the affective system of reactions. This group accounts for the majority of spontaneous recoveries among the anxiety states.

I am grateful to Dr. J. P. S. Robertson for statistical advice and to Messrs. Hulme and Cooper of the laboratory for preparing the chart.

REFERENCES

Curran, D., and Partridge, M. (1952). In *British Surgical Practice. Surgical Progress*, p. 162. Ed. E. Rock Carling and J. Paterson Ross. Butterworth, London.
Lange, J. (1928). In *Handbuch der Geisteskrankheiten*, ed. O. Bumke, Vol. 6. Springer, Berlin.
Lewis, A. J. (1934). *J. ment. Sci.*, **80**, 277.
Mayer-Gross, W., Slater, E. T. O., and Roth, M. (1954). *Clinical Psychiatry*. Cassell, London.
Pippard, J. (1955). *J. ment. Sci.*, **101**, 756.
Rennie, T. A. C. (1939). *Arch. Neurol. Psychiat.* (Chicago), **42**, 877.
—— (1942). *Amer. J. Psychiat.*, **98**, 801.
Ross, T. A. (1923). *The Common Neuroses*. Arnold, London.
Slater, E. (1938). *Z. ges Neurol. Psychiat.*, **162**, 794.

J. Neurol. Neurosurg. Psychiat., 1959, **22**, 342

PROCEEDINGS OF THE SOCIETY OF BRITISH NEUROLOGICAL SURGEONS: 59th MEETING

The 59th Meeting of the Society of British Neurological Surgeons was held at the Royal Society of Medicine, London, as a joint meeting with the Canadian Neurological Society and the Association of British Neurologists on July 14-15, 1959.

The Chair was occupied in rotation by the Presidents of the three Societies, G. S. Clark-Maxwell (Derby), Dr. Allan Walters (Toronto), and Professor F. J. Nattrass (Newcastle). Dr. Earl Walker (Baltimore) attended as the special guest of the Society.

Neuraxial Congenital Dermal Sinuses

W. S. KEITH (Toronto) reported eight cases of lumbo-sacral dermal sinus. Three cases were infected, of which two recovered and one died. He noted that in spite of many publications on this subject during the past 30 years these insignificant lesions were usually overlooked until infection had gained access to the central nervous system. Experience at the Hospital for Sick Children, Toronto, showed that death from this cause still occurred and that there was still a high incidence of damage to the brain, spinal cord, and cauda equina and also severe complications in the urinary tract. All these complications were preventable and a greater awareness of the existence and significance of these lesions was desirable.

Colloid Cysts of the Cervical Canal

R. T. JOHNSTON (Manchester) described in detail two cases of intrathecal cyst of the cervical canal causing cord compression. The cysts were attached to the anterior aspect of the cord by a narrow pedicle, contained colloid, and were pathologically indistinguishable from the colloid cysts of the third ventricle. Their relationship to congenital cysts of the central nervous system in general was discussed, and the question raised as to whether colloid cysts favour predominantly the third ventricle because they originate only in a vestige of a specialized structure such as the paraphysis, or because an error of development at a stage which produces a colloid cyst is more likely to occur in the third ventricle than elsewhere.

Radioactive Encephalography: Automatic Brain Scanning Using Radioactive Iodinated Albumin

WILLIAM FEINDEL, JOSEPH STRATFORD, G. A. B. COWAN, and S. FEDORUL (Saskatoon) reported on the method and results of using an automatic brain scanner in localizing various lesions in the brain.

They noted that a number of radioactive substances had been used recently as indicators of local changes in the blood-brain barrier. Local variations in the uptake of the substances in the brain could then be mapped out by radiation counting devices applied externally to the head. Rectilinear automatic scanning had been developed, particularly by Sweet and Brownell, and detailed studies of collimation had been made by Shy and others. The present report was a review of 70 neurosurgical cases with verified intracranial lesions in which automatic scanning was carried out with twin scintillation counters mapping the head in a spherical pattern. This apparatus, which had been designed by Reid and Johns at the Saskatoon Cancer Clinic, had been in use over the past three years and the advantages and limitations of the method were described.

Aspects of the Behaviour of Human Gliomas in Tissue Culture

T. P. MORLEY (Toronto) reported on the results of tissue culture of human gliomas.

As a basis for future study of gliomas *in vitro*, 60 tumours had been grown in culture and their appearance and behaviour recorded. Certain features might be seen which were characteristic of the group, even though the various types of tumour did not give rise to predictable patterns in culture. Attempts—largely unsuccessful—at transplanting these tumours into rats and mice were reported briefly and information concerning the shedding of glioma cells into venous blood was presented.

The Evolution and Dissolution of Convulsive Phenomena following Head Injuries

A. EARL WALKER (Baltimore) presented a report on the course of patients having post-traumatic convulsive disorders over an eight- to 10-year period. He noted that the incidence of post-traumatic epilepsy did not seem to have lowered, compared with First War figures, in spite of better methods of wound therapy, less infection, and improved treatment for the severely head-injured patient. He wondered, however, whether the populations of the surviving head-injured from the two world wars was the same. Was it not possible that better methods of treatment had saved the lives of severely injured patients, a group in which the frequency of epilepsy was almost 50%?

He stressed the difficulty of making a clear diagnosis in many cases and this was especially true of sudden

attacks of "dizziness". These attacks were commonly scribed to vasomotor instability and although commonly transient might persist for weeks or months. He uggested that inclining the patient on a tilt table whilst aking E.E.G. recordings or suddenly compressing the cular globes might help in diagnosis. The appearance of slow waves associated with syncope on these manoeuvres favoured a vasomotor origin of the attacks.

Even when attacks could be identified as epileptic it was not easy to decide whether the patient should be called an epileptic or not. Such a designation involved important courses of action by the patient, by his medical attendant, his employers, and his lawyer. It was of the utmost importance to know, therefore, if a patient had had one or more attacks which were epileptic, what were the chances of further attacks. In an attempt to answer this question he had studied two series of patients. The first was a series of 244 men seen and studied in detail in 1945-46. All had sustained head injuries, most of them penetrating the brain, and had had one or more convulsive seizures. These had been followed for a period of 10 years. The second series was 732 head-injured men in World War II examined six to nine years after injury. Of these, 207 developed epileptic manifestations. The period of follow-up varied from two to 10 years. The total followed up of the two groups was 435; 16 had died in the interim period.

In the first series of those living, 46·1% had had no attacks for more than two years and 35·6% had had no attacks from the fifth to the tenth year after injury; 14·6% had experienced only one or two attacks per year in the last five years and the remainder were having frequent attacks. This freedom from attacks was not related to medication. Of the second series, 21·1% had had no attacks for five years, 12·1% for two years, 22% had rare attacks, and 43·9% were having several attacks a year.

The frequency of major attacks was less than that of attacks of all types. Many of the patients having minor seizures were so little affected by them that they might be considered as "normal". This spontaneous regression of attacks after head injury had been mentioned by most writers on the subject but had been little emphasized.

The time of cessation of attacks was of interest and in all categories the highest incidence of cessation was in the second and third years. For all types of attack, 20% stopped in this period and about 5% per year thereafter. The incidence of freedom from major seizures was almost double this figure in the second and third years.

Patients with attacks occurring early after a head injury were generally considered to have a better prognosis than those with late attacks. In the first series, patients who had early attacks fared no better than those starting late. This series, however, was probably a selected one and patients who had had early seizures in evacuation units or base hospitals might not be referred to the epilepsy centre. In the second series, however, only 15% of patients who had had an attack within a week of wounding were having attacks six years later; this might be compared with 50% of patients having their initial seizure one to four weeks and 65% of those having an initial attack more than four weeks later.

In the first five years, the cessation or absence of any type of attack for one year was a good omen, for such patients had about four chances out of five of having no more attacks in the next five to eight years. If the patient was free of attacks for two years, the chances of recurrence of multiple attacks was quite slight. Even if the patient had occasional attacks in the first five years after an injury, however, there was still one chance in four that there would be no recurrence of attacks in the subsequent five years.

Frequency of attacks was of prognostic value, those having few attacks in the first five years being more likely to become free of attacks. Although the number of attacks might remain the same, improvement could take place by a shift from major to minor seizures.

Many people had hoped that E.E.G. recordings would give reliable information as to the possibility of epilepsy. From the evidence available he could only conclude, however, that brain waves might denote cerebral damage but they did not reliably indicate or forecast the occurrence of convulsive complications. Hence an abnormal E.E.G. did not mean that a patient had or would have post-traumatic epilepsy. In fact, men having comparable severity of injury, with or without epilepsy, had E.E.G.s of practically identical degrees of abnormality. This was true of records made six months after injury and many years later. In head injuries, therefore, the E.E.G. findings correlated with the degree of severity of wounding which was only one of the determining factors in the genesis of a post-traumatic epilepsy.

Where there was reasonable suspicion of attacks having occurred and a fear that these might recur, he felt it would be better to award the man an insurance policy against recurrence rather than compensation. In closed injuries, the premium should be not more than 1% and in open wounds not more than 10% of the face value of the policy. If he did develop seizures, he would be compensated, if he did not he would not have been stigmatized and the compensating agent would not have paid a penalty.

Even if seizures did develop, it should be clearly understood that they might not chronically recur. In fact, if within the first year or two after a head injury, the patient had had only one or two attacks, he would question the advisability of labelling the condition post-traumatic epilepsy. There was excellent evidence that such patients had a good chance of living a normal life not punctuated by convulsions.

Psychogenic Regional Pain Alias "Hysterical" Pain

ALLAN WALTERS (Toronto) delivered the Presidential address of the Canadian Neurological Society on this subject. He noted that hysterical pain had traditionally meant pain in a bodily part, often with functional tenderness and sensory deficit and with no source of afferent stimulation. When it persisted unrecognized, it might elude diagnosis and defy treatment. A clinical

series of hysterical pain problems from a neuro-psychiatric consulting stream had been reviewed. The range of psychiatric backgrounds extended well beyond hysteria to include most of the neurotic, psychotic, and organic types of reaction. Hysterical pain, then, did not signify hysteria and theories of hysteria might provide only a partial explanation. It was suggested that the term psychogenic regional pain be brought forward into widest usage in place of the term hysterical pain.

This kind of pain was psychogenic in that it might vary independently of the afferent sensory stream, whereas it appeared consonant and appropriate to the way the patient was feeling or behaving. It was regional in that it was perceived remotely from mental activity and localized in a region of contiguous physical tissue. The boundaries of this region, be it area or volume, could not be explained by present knowledge of anatomy or physiology, whereas they seemed to have the attributes of form and symbol in the process of perception. This pain appeared to be a symbol of mental life remotely localized in the somatic perceptual field.

This emphasis on the process of perceptual symbolization as a source of pain raised a context of general problems which were discussed in detail. He noted that such an emphasis under the term psychogenic regional pain might be a more useful basis for the study and treatment of this type of pain in view of our new knowledge and fresh appreciation of the complex processes which were involved in our perception of our pains.

Peripheral Nerve Conduction in Neurological Patients

R. W. GILLIATT (London) said that motor nerve conduction was known to be slow in regenerating nerve fibres (Hodes, Larrabee, and German, 1948), in peripheral neuritis (Lambert, 1956), and in localized compressive lesions such as the carpal tunnel syndrome (Simpson, 1956). Comparable disturbances of sensory nerve conduction had been demonstrated by direct recording from the median and ulnar nerve trunks (Gilliatt and Sears, 1958).

These techniques had now been used to study the long-term effects of operation on the carpal tunnel syndrome. Post-operative examinations on patients with slowing of median nerve conduction at the wrist had been carried out at regular intervals for periods up to two years. Another series of carpal tunnel syndromes treated by splinting of the wrist had been investigated in the same way and a further group treated by local injection of hydrocortisone was being studied in collaboration with Dr. J. B. Foster.

In patients with lesions of the deep branch of the ulnar nerve, Simpson's original observation of a local conduction delay in the hand had been confirmed (Ebeling, Gilliatt, and Thomas, 1960). It was of interest that a lesion in the hand might cause slight slowing of conduction in the proximal portion of the ulnar trunk as high as the axilla: this phenomenon had also been observed in regenerating nerves after suture at the wrist. In mild ulnar lesions at the elbow, motor nerve conduction studies had sometimes been unhelpful, significant abnormalities being found only when recording directly from the ulnar nerve above the elbow during stimulation at the wrist. In such cases, attempts have been made to define the upper level of the lesion by stimulating the nerve trunk above the elbow and recording the arrival of afferent volleys at axillary level.

In the lower limbs it was possible to record afferent volleys from the peroneal nerve and this technique might prove of value in the investigation of patients with mild sensory loss and paraesthesiae in the feet.

In patients with long-standing polyneuritis marked slowing of nerve conduction had been the rule but in Charcot-Marie-Tooth disease the results had been variable and some of his patients had shown normal conduction velocity in spite of gross peripheral wasting.

REFERENCES

Ebeling, P., Gilliatt, R. W., and Thomas, P. K. (1960). *J. Neurol. Neurosurg. Psychiat.* To be published.
Gilliatt, R. W., and Sears, T. A. (1958). *Ibid.*, **21**, 109.
Hodes, R., Larrabee, M. G., and German, W. (1948). *Arch. Neurol. Psychiat. (Chicago)*, **60**, 340.
Lambert, E. H. (1956). In *Clinical Examinations in Neurology*, p. 313. (Mayo Clinic and Mayo Foundation). Saunders, Philadelphia.
Simpson, J. A. (1956). *J. Neurol. Neurosurg. Psychiat.*, **19**, 275.

Broca's Contribution, Reviewed a Century Later

MACDONALD CRITCHLEY (London) discussed Broca's contribution to aphasiology. He noted that until the beginning of the nineteenth century scant attention had been paid to this subject. Articulatory defects were not distinguished from dysphasia and both were confused with incoherency of speech and mutism associated with states of semicoma. Later, physicians began to realize that speech impairment could arise independently of lingual paralysis and that loss of memory for words and names could exist without any concomitant loss of general memory.

The ideas of Gall that mental processes were divisible into rigid compartments and that each aspect of brain function could be correlated with a circumscribed area of the brain were a further stimulus to precise thinking.

Within the interregnum of indecision which these phrenological notions evoked came the classical demonstration by Broca.

He then described the events surrounding this demonstration and the discussions which followed it. He stressed the fact that the part played by Dr. Ernest Auburtin in this important event was often overlooked.

He noted that Broca's contribution triggered off a belief that speech disorder was a focal symptom in brain disease, and by implication that the normal faculty of speech possessed a cerebral "representation" of a limited punctate character.

Although many neurologists were utterly unimpressed by such over-simplification, they did not make a direct attack upon the materialists' notions and it was only within the last decade or so that more general dissatisfaction had been expressed. Not even had a rigid ascription of speech function to purely left-brain activity and speech dysfunction to left-brain disease been wholly accepted and the role of the minor or non-dominant hemisphere was no longer inadmissible.

A final remark was necessary as to the problem of

dysphasia versus dysarthria. Originally regarded as more or less identical, they became sharply distinguished by Jackson and his contemporaries. After several changes of view in the intervening years, contemporary ideas once again tended to swing away from too rigid a cleavage between disorders of language. It was now recognized that in aphasic utterance there might be a considerable upset in phonemic patterns, but furthermore, cases of inborn articulatory defect might lead to a stunting in the free growth of the faculty of language. Lastly, the notion of articulatory apraxia—once enthusiastically acclaimed, later discredited—had once again become mooted as a factor in acquired affections of speech.

A Symposium on the Results of Modern Treatment of Head Injuries

C. E. G. GOULD (Vancouver) stated that once the severity of damage, in terms of depth and duration of altered consciousness, length of retrograde amnesia, degree and duration of confusional state, condition of the spinal fluid, and precise information as to local damage had been appraised a prognosis could be formulated. He wished to elaborate, however, on certain factors that had no relationship to the above criteria but which might exert a profound effect on prognosis.

Amongst these factors could be mentioned the premorbid personality of the patient and the litigation factor. Frequently a potent influence was exerted on a patient by a marital partner, members of the family, or friends. These influences often "froze" a patient into a pattern of reaction to injury where function was below the level predicted on a solely organic basis.

A particular problem in Canada was the immigrant who had not been successfully assimilated into the country of adoption. In such cases one frequently saw a paranoidal reaction directed towards the insuring body.

In older patients, where head injury had been incurred at work, and especially when the work was of a hazardous nature, the motivation to return to work was weak.

When assessment of the rôle these factors might be playing in a given case was added to the assessment of severity of injury in organic terms, the picture could become complex to the point where prognosis was difficult and frequently inaccurate.

W. RITCHIE RUSSELL (Oxford) said that every new discovery in cerebral physiology became applied to the study of brain injuries and the experiences of the past 50 years reflected many changing attitudes. One could recall the old emphasis on microscopic lesions in the brain-stem, the concept of acute compressive anaemia of the brain, the period of treatment by intensive dehydration or by routine craniotomy in relation to fractures. It was generally agreed now that the chief effect of head injury in acceleration concussion was a physical disturbance of neurones caused by shearing and distorting waves of force throughout the brain. Strich's recent demonstration of widespread tract destruction in cases of traumatic dementia was most significant in this regard.

The most important advance in treatment in recent years had been concerned with protecting the lungs from inhalation during coma. First aid workers now transported these patients in the semi-prone position and when difficulties persisted tracheotomies were done in hospital.

Recent interest in the brain-stem in relation to consciousness had led to a belief that damage here was the chief cause of coma, but it should be pointed out that the hemispheres were much more vulnerable and if widely concussed were just as likely to inactivate the brain-stem centres as the other way round. The application of hypothermia to severe injuries was of great interest but should be watched very critically. A reduction of, say, the degree of decerebrate rigidity, meant that the nerve cells involved were being inactivated by cold, but when exactly this was advantageous must be very difficult to judge.

In recent years his special interest had been concerned with the rehabilitation of cases of head injury. Wartime experience demonstrated the importance of a vigorous programme of physical training, and it was regrettable that the standard of rehabilitation of civilian injuries was in many places so low. Good rehabilitation prevented the post-traumatic neurosis from developing, but it must be realistic; there was no such thing as complete recovery from severe head injury, and the patient must understand this.

G. F. ROWBOTHAM (Newcastle) said that it was well known that the clinical picture of a head injury resulted from a complex of interacting factors that arose both within and outside the head. He was concerned with an attempt to break up this complex and to focus attention on those factors that arose directly from the injury to the brain itself. Such a study was important in the context of this discussion since, given adequate treatment, the final outcome of any head injury must depend on the nature, the site, and the extent of the intracranial injury.

He was concerned on this occasion with post-mortem findings but mentioned operative findings, clinical features, neurological adductions, and animal experiments as other important methods of investigation.

His material consisted of a series of 50 brain specimens from patients under his care who had died from head injury. The brains had been removed and the extent and size of surface haemorrhages noted. They were then cut in coronal section and lesions photographed. Histological examination was made of the brain-stem and post-mortem findings correlated with clinical signs. (An extensive series of brain sections was then demonstrated.)

He realized that these sections demonstrated extreme degrees of injury but stressed that they probably represented in kind similar injuries which did not come to necropsy. It could be concluded from this material that the cerebral hemispheres were more likely to be damaged than the brain-stem and that lasting physical morbidity was largely hemispheral in origin. He thought that brain-stem syndromes were due, in the majority of cases, to hemispheral damage or swelling and not to intrinsic brain-stem damage. Brain-stem syndromes due to

brain-stem damage were invariably fatal. He stressed that damage to the corpus callosum was common and probably played a significant rôle in the clinical picture and morbidity. He noted also that acute subdural haemorrhages were common and often of sufficient size to compress the brain, and could lead to severe and long-lasting head pains. The incidence of damage to large arteries with infarction was small but when it did occur gave rise to long-lasting morbidity.

Discussing the mechanisms of unconsciousness in head injury, he agreed that there was, as yet, no proof that the cerebral hemispheres were essential for consciousness and that injury to the brain-stem could cause unconsciousness. He thought, however, that it was possible that paralysis of function in both hemispheres could cause loss of consciousness and if this were so, then in head injuries he considered that the seat of unconsciousness was hemispheral and not brain-stem.

E. Bruce Hendrick (Toronto) reviewed a series of 1,997 cases of cranio-cerebral injury admitted to the Neurosurgical Service of the Hospital for Sick Children, Toronto, between January, 1955, and December, 1958. The major forms of injury were discussed briefly. Special attention was paid to the treatment of severe head injuries with hypothermia and to the diagnosis and handling of extradural haemorrhage in children.

A. N. Guthkelch (Manchester) considered some of the special problems related to head injuries in children and arising from a group of 590 cases admitted to the Royal Manchester Children's Hospital. He stressed the fact that in the mild case diagnosis was difficult and in 43 cases there was no record of head trauma, the only presenting feature being that the child had vomited after an accident. In another group of cases the child fell over and then had a generalized convulsion. Undoubtedly, some of these cases were of simple epilepsy and the head injury secondary to the fit.

The incidence of epilepsy was 5%, including cases with a single fit, the incidence of persistent post-traumatic epilepsy was 1·2%. The incidence was higher, 7% in cases of compound depressed fracture. From this series, however, it would seem that widespread brain damage was more important than a focal lesion, for in the group of cases with more than seven days' disturbance of consciousness, the incidence of epilepsy was 25%.

Post-concussional symptoms were not often a problem and its frequency varied with the severity of the injury. Contrary to usual belief intracranial haematomas were not uncommon in children, and in this series 12 extradural, 13 subdural, and five intracerebral haematomas were treated. All but one case of acute subdural haematoma made good recoveries.

He drew special attention to a group of injuries around the orbit; these might be more serious than was at first suspected. In four cases sharp objects had penetrated the cranial cavity through the orbit. This penetration was unsuspected at first with the result that one case developed clot compression, one meningitis, and two cases developed brain abscesses. In two cases injury to the soft tissues around the orbit resulted in cerebral thrombophlebitis and epilepsy. In four cases a haematoma in the orbital area without demonstrable external injury or fracture led to intracranial infection.

There were 11 deaths in the series (1·9%) most being due to primary brain damage. In three, necropsy revealed widespread anoxic changes; tracheostomy might have saved them. Two deaths followed air encephalography.

Joe Pennybacker (Oxford) reported the results of a questionnaire circulated by the Society amongst its members in January, 1959. The object of the enquiry was to determine what proportion of head injuries in the United Kingdom were "covered" by neurosurgeons and to assess the value of special methods of treatment such as tracheostomy, hypothermia, and dehydration. The present report was a preliminary analysis of the returns which appeared to indicate that, with a few exceptions, neurosurgical cover was inadequate and facilities for convalescence and rehabilitation needed expansion. The rôle of the general surgeon in head injuries was discussed and it appeared that the most important practical step which could be taken now was to train young general surgeons in the few special techniques applicable to head injuries.

The replies as to special methods of treatment indicated general agreement that tracheostomy was valuable, but there was less certainty as to the value of hypothermia and dehydration. The prognosis in cases of prolonged coma was discussed, and although it appeared that modern methods of treatment were saving more lives in the acute stage to be followed by prolonged coma, the numbers had not yet reached serious proportions.

Intervertebral Disc Protrusions in Childhood and Adolescence

J. E. A. O'Connell (London) said that experience of intervertebral disc protrusions in childhood and adolescence had been confined to those occurring in the lumbar region. The records of 38 patients with such protrusions and aged 17 years or less were reviewed and the findings compared with those of an earlier analysis of 500 cases of lumbar disc protrusion unselected as regards age.

While the aetiological factors in adolescence were similar to those in later life, it was pointed out that the maximum age incidence of adolescent protrusions differs in the two sexes and corresponds to the period of most rapid development in each. The stresses occasioned by growth may thus be of aetiological significance.

The symptomatology in the young patients resembled that in adults, but adolescents might complain less of pain although their symptoms tend to be more persistent. No case in the series developed a severe subjective defect of function. The spinal signs and those of tension in the roots of the sciatic nerve were frequently more severe in the young patient, while the neurological ones were less frequent and less severe than in adults. Radiological abnormality was frequently absent.

Other lesions in the lower portion of the spinal canal or involving the lumbo-sacral portion of the spine were

important in differential diagnosis. Of the former, intraspinal neoplasms were the most important, but meningoceles of the extradural nerve produced a clinical picture identical with that of disc protrusions. Of the vertebral lesions, spondylolisthesis and ankylosing spondylitis were the most important. Arthritis of the apophyseal joints occasioned a picture almost identical with that of a disc protrusion in one patient. Although it was at one time always suspected in adolescents exhibiting the clinical picture which has been described, no case of tuberculous spondylitis had been encountered.

At operation, the last intervertebral disc or the penultimate one was involved in every case. The protrusions were composed of soft elastic disc tissue with a high fluid content, and on the average were larger than in adults.

The results of surgical treatment were good, 91% being either cured or greatly improved. Recurrence of symptoms required re-operation in 6% of cases.

The different clinical picture in adolescents might be due to the mobility of the spine in early life. Muscle spasm due to the stimulation of the hyperirritable extradural nerve by the large soft protrusion might induce severe deformity and limitation of spinal movement and straight leg raising. This protected the extradural nerve from injury and neurological signs were therefore mild or absent.

Therapy in Carotid Artery Disease

H. J. M. BARNETT and W. H. LOUGHEED (Toronto) presented a study of a substantially large series of patients proven arteriographically to be afflicted with carotid thrombosis or stenosis. The therapeutic problems posed by this group were discussed.

The most impressive result of the study was the need that it pointed to for early diagnosis. The difficulty encountered in distinguishing carotid artery disease from middle cerebral artery disease on a clinical basis had led them to conclude that one could not with any certainty discuss "carotid artery syndromes" and their therapy unless referred to pathologically or radiologically proven cases. On the other hand, the inefficiency of arteriography in determining clinically significant collateral and contralateral blood flow to the brain was remarked and illustrated.

Their experience with anticoagulant and surgical management of these cases was outlined. The hazards of embarking on surgery without an arteriographic survey of the total problem were presented. The complicating factor of greatest importance was the coincident occurrence of intracerebral carotid as well as basilar-vertebral disease.

A Controlled Clinical Trial of Anticoagulant Therapy in Cerebrovascular Disease

JOHN MARSHALL (London) described a clinical trial of anticoagulant therapy in cerebrovascular disease. The aim of the trial was to see if long-term anticoagulant therapy reduced mortality, prevented further strokes, and improved the functional capacity of the patients. One hundred and forty-two patients were in the trial, 71 on anticoagulant therapy and 71 as controls. There was no significant difference in the incidence of further non-fatal cerebrovascular accidents, but the incidence of fatal cerebral haemorrhage was significantly higher in the treated group, hence the trial was stopped.

The Surgical Treatment of Primary Intracerebral Haemorrhage

WYLIE MCKISSOCK (London) presented a survey of 240 patients who had suffered a primary intracerebral haemorrhage, presumably due to rupture of an atherosclerotic vessel, and had been treated surgically. The very variable modes of onset were described and the difficulties of purely clinical diagnosis emphasised. Angiography was used in 167 cases but proved diagnostic in only 70% so that recourse to burr holes, often followed by ventriculography, was often necessary to establish the diagnosis. The absence of bleeding into the ventricular system or subarachnoid space in 20% of cases was commented upon.

Patients were treated by burr hole and aspiration (104), aspiration and later craniotomy (73), and craniotomy alone (31). Of the 208 patients treated, 106 died within three weeks. Follow-up of the 102 survivors for periods of one to 10 years revealed 31 deaths. Ten were from progression of the disease in periods of one to three months and five from further cerebrovascular accidents. In the remainder the cause of death was either unknown or from some other disease. Of the 63 survivors, 25 were well and leading a normal life, 14 had minimal disability, 18 were moderately disabled, and six totally disabled.

Age did not influence the chance of survival but situation of haemorrhage did. Capsular haemorrhages rupturing into the ventricular system and basal ganglia carried an almost 100% death rate. Those patients in coma had a 100% mortality whilst in those who were alert the death rate was 23%.

Cerebellar lesions formed some 10% of these cases and although they posed difficult diagnostic problems they were amenable to surgical treatment.

He stressed the fact that a controlled trial of surgical and medical methods of treatment was necessary to establish the correct course of action in this pathological condition.

BOOK REVIEWS

Topométrie Cranio-Encéphalique chez L'homme (Cranio-Cerebral Topometry in Man). By A. Delmas and B. Pertuiset. (Pp. 436; 121 figures, 187 sectional drawings and photographs. £14.) Oxford: Blackwell Scientific Publications; Paris: Masson et Cie. 1959.

This is a beautifully produced volume designed to aid the stereotaxic worker in his search for the location in space of intracerebral structures. This problem is rendered more difficult by the individual variation in these structures. Correlation between the location of subcortical structures and the cephalic index are presented, determining the spatial limits of any given individual structure in relation to standard cerebral planes. The limits can be derived from either graphs or equations given in the book, based upon statistical analysis of measurements of 21 subcortical structures in 14 subjects. The authors note, and one would agree, that it is surprising that meaningful conclusions can be drawn from a study of such a small series, but the validity of the deductions is based on Fisher's work on the probabilities of small series analysis. The book in addition contains a useful atlas of drawn and photographed cerebral sections. A short review of the statistical theory upon which the work is based is helpful, and there is a useful anatomical catalogue and alphabetical index of anatomical structures. The work is particularly valuable as it is for general purposes and not designed for use with any one particular stereoencephalotome. The text is in both French and English.

L'Angiographie Cérébrale. By Joël Bonnal and Jacques Legré; Foreword by Prof. J.-E. Paillas. (Pp. 254; 223 figures.) Paris: Masson et Cie. 1958.

There are not many textbooks on this subject and Bonnal, a neurosurgeon, and Legré, a radiologist, both from Marseilles, have covered the field well. The illustrations and line drawings are of a high quality, but it is unfortunate that all the radiographs are positives. However, this practice is by no means confined to French publications.

After introducing the subject by describing the technique, indications, and dangers of angiography, the authors outline the normal angiographic appearances, both of the carotid and vertebral trees. This is followed by the largest chapter, which is devoted to neoplasms. The other chapters concern aneurysms and angiomas, obliterative lesions of the main vessels, and finally a few miscellaneous conditions.

One is a little shocked by the illustrations in the chapter on technique. It seems that the protection of the operator and his assistants from ionizing radiation consists only in the use of a long connecting system between the injecting syringe and the intra-arterial needle. There is no suggestion of using lead-rubber protective screens.

The bibliography is adequate but not exhaustive. It is gratifying to find work quoted from a number of countries, but the large majority of references are continental European.

The book is to be recommended as one of the best of the recent publications on cerebral angiography.

Temporal Lobe Epilepsy. A colloquium presented under the auspices of the U.S. National Institutes of Health, 1957. Edited by Maitland Baldwin and Pearce Bailey. (Pp. xiii + 581; illustrated. £5 17*s.* 6*d.*) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

This monograph contains the reports and discussions of the Second International Colloquium on Temporal Lobe Epilepsy held in 1957 at the U.S. National Institutes of Health, Bethesda, Maryland, under the leadership of Earl Walker and Henri Gastaut. It follows on the reports in the *Acta Medica Belgica* of the first colloquium which was held at Marseilles in 1954. Many contributors who are among the leaders in this field in north and south America and in Europe have taken part, and the volume consists of some 33 separate papers with the subsequent discussions. It has been arranged in four parts starting with the neurophysiological and electrophysiological aspects, and thence progressing through neuropathology and neurochemistry before coming to the surgical aspects. The final section deals with the clinical and psychological effects of temporal lobe ablations both in man and in animals. Most of the reports are short and several are excellent, but it is inevitable that some papers overlap and that contrary views are given. Still, the monograph contains such a wealth of information that it is likely to be a reference book for those interested in epilepsy. The aspects in which the information is somewhat sparse concern the historical development of the concept of temporal lobe epilepsy, its treatment by anticonvulsant drugs and other medical régimes, and its importance in psychiatric practice.

Chronic Subdural Hematoma. By Ragnar Nordlie. (Pp. 164; 24 figures.) Oslo: Johan Grundt Tanum Forlag. 1958.

This short monograph brings up for discussion the problems in the recognition and management of chronic subdural haematomas. It follows the Scandinavian custom of taking some 52 personal cases (43 chronic and nine acute subdural haematomas), and comparing their symptoms, diagnosis, and treatment with views expressed in the literature. The author propounds the view that his condition should not remain undiagnosed only

to be disclosed at some cranial exploration. Instead by a careful analysis of the symptoms supplemented by radiological examination, and in particular by carotid arteriography, all these lesions should be disclosed before operation, so that operation itself becomes definitive treatment and not an exploratory procedure. The author deals chiefly with chronic subdural haematomas in adults but also touches on haematomas of infancy. He gives a comprehensive survey of the literature, and draws our attention again to the condition without adding much new information.

Dégénérescence Hépato-Lenticulaire. By Georges Boudin and Bernard Pépin. (Pp. 250; 46 figures. Fr. frs. 3,500.-.) Paris: Masson et Cie. 1959.

This short monograph on Kinnier-Wilson's disease provides a useful survey of the clinical manifestations of the condition. The authors review fully both the neurological and other findings in the disease. They summarize but do not critically assess modern knowledge of the biochemical background presumed to be the cause of the condition—the abnormalities of copper metabolism as represented by a reduced or absent copper-carrying protein, caeruloplasmin. They also mention treatment with B.A.L., chelating agents, and penicillamine and *en passant* by transfusion of the missing caeruloplasmin. None seems to have any but a temporary effect. The value of the book is in bringing together and reviewing the scattered literature both old and new on this subject and in comparing it with the author's own clinical experience of the disease.

Pain, 2nd ed. By Harold Wolff and Stewart Wolf. (Pp. 121; 20 figures. 32*s.* 6*d.*) Oxford: Blackwell Scientific Publications. 1959.

This short book, now in its second edition, is devoted mainly to a brief consideration of the anatomical and physiological background of pain. This it does reasonably well—especially in discussing the mechanism of headache, a subject on which the authors have done much original work. "Thalamic" or "central" pain is an important entity clinically because it is both distressing and intractable: but neither its description nor its possible physiological background are well covered. The description of referred pain is adequate but its possible mechanism is hardly discussed. The section on management of pain is rather disappointing: though the student can derive for himself some aspects of treatment from the anatomical and physiological considerations mentioned, little direct help is given to the clinician who has to deal with these cases.

Neuroftalmologia. By P. Ottonello and G. W. Vassura. (Pp. 611; 149 figures. Lira 15,000.-.) Bologna: Cappelli Editore. 1959.

The authors have written this book in two parts. In the first each chapter is devoted to one aspect of neuro-ophthalmology, visual fields, ocular movements, nystagmus, the pupils, the sensory innervation, and methods of examination. In the second part the effects on the eye of lesions in various parts of the nervous system and by various types of disorder are discussed. The whole is liberally and clearly illustrated, with colour plates where necessary, and the presentation is clear. The printing and paper are very satisfactory, but the binding could usefully be stronger.

Psychological Stress: Psychoanalytic and Behavioral Studies of Surgical Patients. By Irving L. Janis. (Pp. xiv + 439. 56*s.*) New York: John Wiley (London: Chapman & Hall). 1958.

In his introduction the author indicates how little we know regarding objective anxiety compared with our knowledge of neurotic anxiety. He then describes research he has conducted into effects of stress, the stressful situation being a surgical operation.

In the first half of the book the author describes and discusses the psychoanalytic sessions of a patient, who, in the course of psychoanalysis, had to have an operation on her leg. On the basis of these studies he puts forward a number of hypotheses and propositions dealing with the causes and consequences of various types of emotional reactions and adjustment mechanisms which are frequently activated when people are exposed to severe environmental dangers.

The second half of the book consists of a study of 22 patients undergoing operations, and also a survey by questionnaire of 150 Yale students regarding their experiences of operations they had had. Perhaps the most obvious conclusion that the author draws is that "informed" patients, patients who have had the nature of the operation explained to them, have less fear than the "uninformed". They are also less likely to become emotionally disturbed post-operatively, showing this by breaking rules or getting angry. On the basis of these and other findings advice is given on the psychological preparation of patients for operation.

Geniale Menschen, 5th ed. By Ernst Kretschmer. (Pp. viii + 311. DM. 36.-.) Berlin—Göttingen—Heidelberg: Springer Verlag. 1958.

The author, well known for his psychiatric analysis of the relationship of body type and character, has investigated the biological laws, the motivations, and personality trends which might explain the creative powers of outstanding personalities referred to as Genius. Kretschmer's biographical and psychoanalytical account of famous politicians, poets, scientists, and musicians is fascinating and instructive and should attract psychologists, psychiatrists, and the general reader interested in biographical sketches.

Personality Patterns of Psychiatrists: A Study of Methods of Selecting Residents, Volumes I and II. By Robert R. Holt and Lester Luborsky. (Pp. Vol. I, xiv + 386; $7.50; Pp. Vol. II, xiv + 400, $4.00.) New York: Basic Books. Menninger Clinic Monograph Series No. 13. 1958.

After the last war, there was a vast (and to judge from the data in these volumes, much needed) expansion of

psychiatric services in the United States. This necessitated the training of large numbers of psychiatrists and a large proportion were trained at the Menninger School of Psychiatry, said to be the largest training centre for psychiatry in the world. The selection of applicants for training was made a research project to determine the qualities desirable in a psychiatrist. Applicants were interviewed and were given intelligence tests, projection tests, and personality inventory tests. On the basis of these, attempts were made to ascertain the personality qualities required in a psychiatrist.

All this is very salutary and such a basis of selection may ultimately be preferable to the somewhat haphazard methods of selection used in this country. However, so far as practice in this country is concerned, this book contributes little of value. The emphasis throughout the book is on the superiority of psychotherapy: this attitude of the School must have played some part in the self selection of applicants. We read, for example, that of the 238 residents in the series, 22% sought and received psychotherapeutic help, and an additional 43% sought treatment but did not get it. Only 35% of the residents apparently did not consider they needed psychotherapy. One must bear in mind that in this topsy-turvy world to be receiving psychotherapy was to have a certain social *cachet*. The attitude of the School is also revealed perhaps by the fact that the best residents (the steady highs) ended doing psychoanalysis: the poorest residents (the plodders and the incompetents) ended doing shock therapy. Even more revealing are the errata. There are 10 errata, seven of which consist in substituting "psychotherapeutic" for "psychiatric". This observation is offered gratis to psychopathologists of everyday life.

Recent Progress in Psychiatry, Vol. 3 (*Journal of Mental Science*). Edited by G. W. T. H. Fleming and A. Walk. (Pp. 397. 42*s*.) London: J. & A. Churchill. 1959.

The third volume of "Recent Progress in Psychiatry", although published in 1959, covers the quinquennium 1950 to 1955. Despite the delay in publication, it is a valuable book to the psychiatric practitioner and postgraduate student. The period it covers was one of active development in several important fields; thus sections are devoted to subjects such as cybernetics, the organization and connexions of the hippocampal and intralaminar systems, and the enzymatic basis of certain psychoses. At the same time there are serious omissions in the subjects represented. For instance, there is no chapter on the therapeutic use of drugs in psychiatry, a field in which major progress has been made in recent years.

The primary aim of most of the contributors has been an impartial and wide coverage of the scope of their subjects. In a book of this kind, which is chiefly intended as a source of reference, this is more important than an attempt at subjective evaluation, in which the writer is swayed by his own interests, giving an incomplete and possibly seriously prejudiced account of the advances made in his subject. This choice of approach has been faced squarely by the "Professor of Psychiatry, Institute of Psychiatry (Maudsley Hospital)" (*sic*) in the section entitled "Personality Tests: 1950-1955". Professor H. J. Eysenck admits frankly that the number of publications germane to this subject is so great that "any attempt at even reasonably complete coverage of different aspects would be quite impossible", and he reviews those trends which he himself considers to be the most important. The reader slightly acquainted with personality testing, a subject fraught with controversy, is left with the uneasy feeling that perhaps no bread would have been better than the half loaf.

This book would have been better for more economy in editing. For example, the same subject matter is covered competently and in considerable detail with respect to mongolism in the chapters on psychiatric genetics and mental deficiency. The individual authors cannot be blamed as in most cases they try to cover the full range of the subject they have been asked to review, and they succeed in doing this concisely and with clear definition.

Thus the chief faults of this book are deficiencies in overall planning and editing. The individual contributions are, for the most part, comprehensive, instructive, and enjoyable to read. On the whole it gives a clear picture of recent progress in the fields of psychiatry under review, and with the excellent bibliographies it contains it should prove an extremely useful book of reference.

Amphetamine Psychosis (Maudsley Monographs No. 5). By P. H. Connell. (Pp. 133; 25 figures, 22 tables, 11 photographs. 21*s*.) London: Chapman and Hall. 1958.

Accounts of drug intoxications which mimic naturally-occurring psychoses are always of interest, because of their physiological implications and because they engender a little optimism over the prospects for therapy in the future. This study of the schizophrenia-like illness produced by amphetamine is concerned with 42 cases, and is a commendable addition to the Maudsley Monographs. It is based on a thesis for the M.D. and it is both informative and readable. The description of the clinical condition is excellent. The frequency of this intoxication makes it important in differential diagnosis. The prognosis is good if the addiction and source of supply of the drug can be discovered. The author produces a careful array of facts to show that amphetamine psychosis is not merely an exposure of pre-existing but concealed mental disorder. He is also most careful not to draw conclusions about the relationship between the drug-induced and natural illnesses.

The second part of the book is devoted to the evaluation of analytical methods which have obviously been of great service in confirming the diagnosis and in following the course of the addiction. There is no index.

Ataractic and Hallucinogenic Drugs in Psychiatry: Report of a Study Group. *Wld Hlth Organ Tech. Rep. Ser.* No. 152. (Pp. 72. 3*s*. 6*d*.) London: H.M.S.O.; Geneva: World Health Organization. 1958.

This report was prepared by a small international

group of psychiatrists and others convened at Geneva in November, 1957, under the Chairmanship of Professor E. Lindemann, of the Harvard Medical School. Their terms of reference were to examine, in a preliminary way, the present state of knowledge—and ignorance—regarding the mode of action and effects of psychotropic drugs, and their current applications in psychiatry.

Although admittedly preliminary, this report does provide a useful and well-considered survey of a field in which it is particularly difficult for those standing outside it to distinguish fact from fashion. The authors have some interesting and useful things to say about the design and methodology of drug research and about the importance of racial and cultural factors in relation to psychiatric disorder and its treatment by physical methods. They also stress the obvious need for a clear and well-defined terminology.

In spite of the competence with which the authors of this report have done their work, it is clear that a great deal more basic research in neuropharmacology will have to be carried out before any very adequate rationale for the use of psychotropic drugs in psychiatry is likely to emerge.

Carbon Dioxide Therapy, 2nd ed. Edited by L. J. Meduna. (Pp. xii + 541; with figures and tables. £5 10*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

Carbon dioxide therapy is used as a treatment for psychoneurosis, and consists in making the patient respire a gas containing a high proportion, say 30%, of carbon dioxide. This is continued until consciousness is lost, and is repeated at intervals. This book, a collaborative effort of members of the Carbon Dioxide Research Association, sets out to describe the theory and technique of treatment, and the clinical, physiological, and psychological consequences of its use. The treatment was inspired by the success of physical measures for the treatment of the psychoses. It seemed probable to Dr. Meduna that physical factors that affect the brain must also affect the mind (though he is disinclined to distinguish too sharply between brain and mind) and he tried first with various concentrations of carbon dioxide. There is now a considerable body of psychiatrists employing this treatment, and many of them report their experiences with illustrative case records, though it is difficult to assess the results of treatment in such patients without a prolonged controlled trial.

Mental Deficiency: The Changing Outlook. Edited by Ann M. Clarke & A. D. B. Clarke. (Pp. xvi + 513; 4 figures, 26 tables. 45*s*.) London: Methuen. 1958.

This book provides a most valuable record of recent research work on the factors which influence the development of mental deficiency. There is at present a great variety of specialists taking an interest in how the brain develops, and those who are relatively ignorant of the important work by psychologists in this field will find the book most valuable.

Special emphasis is laid on the importance of the environment in the early months of life, on the development of intelligence, and of satisfactory behaviour patterns. Most of the work described is of the greatest importance from the point of view of education in its widest sense, and the authors rightly stress the great need for research in this difficult field.

Mental Health Aspects of the Peaceful Uses of Atomic Energy, Report by a Study Group. W.H.O. Technical Report Series, No. 151. (Pp. 53. 3*s*. 6*d*.) London: H.M. Stationery Office. 1958.

This report is interesting and entertaining: interesting as an illustration of how little can usefully be said on the subject, entertaining for the verbiage used to fill the lacunae. No terms of reference are quoted for the study group producing the report. In its compilation the members of the group would appear to have employed the method of free association on the wording of the title. Opening with the unexceptionable if somewhat diffuse statement:

> "The history of mankind shows with what flexibility and with how great a measure of success humanity has adapted itself again and again to very radical changes in its living conditions" it concludes "But in the long run the greatest hope of mental health in the future of the peaceful uses of atomic energy is the raising of a new generation which has learnt to live on terms with ignorance and uncertainty . . . ."

Before reaching this peroration, however, its 45 pages are scattered with such important statements as "The general public of the whole world is a concept so vast that an attempt to make generalizations would be of no value", "Many people in government, and many elected representatives, have a feeling that Pandora's box has been opened, and that anything can happen now", "in part, the authorities are in the same position as the general public and, in part, have special problems, owing to the demands and insecurities of their position".

It is a pity this report was published. It will cause many intelligent readers (medical and lay) to wonder how such a potentially important subject can be treated with such a wealth of flatulent platitudes: and such thoughts may extend to the World Health Organization which in some of its activities has done and is doing much useful work.

Catechism Series: **Mental Disorders,** 5th ed. By W. S. Dawson. (Pp. 68. 2*s*. 6*d*.) Edinburgh and London: E. & Livingstone. 1958.

The Catechism series is well known to all students, and the fifth edition of the booklet on psychiatry has the advantages and faults of its predecessors. The main advantage is that the book contains questions of a kind likely to be asked in vivas: the main fault is that the answers are not likely to satisfy examiners who have an unfortunate habit of putting supplementary questions. For revision purposes, however, this booklet is valuable.

Topics in Psychiatry. Edited by T. Ferguson Rodger, R. M. Mowbray, and J. R. Roy. (Pp. x + 265. 20*s*.) London: Cassell. 1958.

This book is an edited account of papers presented at a Specialist Conference in Psychiatry held in Glasgow

in 1957. Topics discussed were schizophrenia, psychosomatic medicine, tranquillizing drugs, mental deficiency, and biochemistry and genetics. The intention was to provide a survey of some of the newer developments in these fields and to stimulate a rapprochement between different viewpoints. In this the contributors have succeeded admirably, and the book can be strongly recommended as containing much information regarding recent advances in a palatable form. The standard of the contributions throughout is high and it would be invidious to single out any for special commendation. The contributors were mainly from the west of Scotland and this book illustrates the lively state of psychiatry in this region.

Cure de Sommeil Collective et Psychothérapie de Groupe. By Henri Faure. (Pp. 272; 5 figures. Fr. frs. 2.500.-.) Paris: Masson et Cie. 1958.

The author describes a novel method of sleep treatment or rather, prolonged narcosis. Patients are treated in groups of five to seven for a period of three weeks. Narcosis is induced by barbiturates and chlorpromazine, the "cocktail" being administered thrice daily so that there are three periods of sleep. Between these periods there are intervals of two hours or so when patients have their meals and toilet and medical procedures are carried out. Also during these periods, the doctor who is in charge of the group encourages them to talk about themselves, their dreams, and their thoughts. The patients also receive individual psychotherapy.

After describing the practical details of the treatment, the author discusses the dreams and thoughts expressed by the patients, the group and individual psychotherapy which the patients receive, and the value of this method as a treatment and as a means of psychological investigation of the individual patients.

The results of treatment in 142 patients are given. Except for schizophrenia where none of 18 patients was helped, the results are comparable with those obtained by more orthodox methods and the treatment is perhaps more economical of medical man-power than most others.

Das Hirngeschädigte Kind: Psychologie und Diagnostik. Eine experimentelle Untersuchung. By Karl-Hermann Wewetzer. (Pp. viii + 117; 9 figures. DM 19. 80.) Stuttgart: Georg Thieme. 1959.

This book reports an investigation in which systematic, standard, psychological tests were applied to a group of children with varied brain pathology and to a similar number of healthy individuals matched in age and general intelligence to the experimental group. The object seems to have been less the elucidation of functional disturbances attendant on any particular type of cerebral pathology than the development of a technique of diagnosis differential as between organic brain damage and other causes of educational and social shortcomings in children. The tests employed range from those familiar in British and American practice such as the Binet, Bender-Gestalt, and Koh's block, to the Strauss and Kephart character appraisal. Considerable industry and care is displayed in the statistical treatment of the results, which is pressed as far as factor analysis. But perhaps the most interesting conclusion is that, while in "brain-healthy" children no particular relation subsists between intellectual and affective features of their test behaviour, in those with cerebral pathology there is a marked connexion between these two aspects. The author's attribution of this to a disturbance of "*Grundfunktion*" may or may not be viable. But the finding itself perhaps merits the attention of anyone who is content to treat motivation as a footnote to intellectual performance.

Personality Change and Development as Measured by the Projective Techniques. By Molly Harrower. (Pp. 383; heavily illustrated. $10.00.) New York and London: Grune and Stratton. 1958.

Projective techniques have an insecure yet tenacious hold on the skirts of applied psychology. The attractive assumptions on which they are based, and the perennial demand for some means of recording and delineating personality ensure their widespread use but cannot ensure acceptance of their validity. The present study is by one of the most prominent and experienced workers in this field. Dr. Harrower has accumulated during the last 15 years the responses of some 4,000 subjects to a combination of projective tests which include the Rorschach, Szondi, thematic apperception, sentence-completion, and "most unpleasant concept" tests. The findings obtained on more than one occasion were evaluated in respect of each subject's productivity, relation to reality, thought content, constructive fantasy, anxiety, and intelligence level.

The investigation was designed to ascertain how far projective test findings mirror clinically detectable changes, and whether they differentiate between improvement brought about by psychological treatment and improvement that occurs without such intervention. The answers, which were provided by the evidence here presented in painstaking detail, amount to a weak and unimpressive "Yes" to the first question, and a fairly definite "No" to the second.

A Textbook in Rorschach Test Diagnosis. By Ewald Bohm. Translated by Anne G. Beck and Samuel J. Beck. (Pp. xi + 322. $7.75.) New York : Grune and Stratton. 1958.

Devised in Switzerland and widely adopted throughout the world, the Rorschach test attained its maximum popularity in the United States, where it has also suffered its sharpest decline. It is, however, still much employed by clinicians, and this manual reviews in a systematic way the considerable volume of work on the Rorschach test published in European countries. The Scandinavian psychiatric literature is particularly well represented. After a brief introduction the technique of administration and scoring is fully described: then comes the largest part of the book, which deals with interpretation. As in most Rorschach publications, the weakest feature is in the attempt at impartial assessment of the test's power

to delineate personality and to differentiate varieties of mental disorder. As a convenient guide to European studies, this book supplements usefully the familiar texts by Klopfer and Kelley, Bockner and Halpern, and Beck (the translator of the present work). It is well translated.

Symposia on Child and Juvenile Delinquency (presented at the American Orthopsychiatric Association). Edited by Benjamin Karpman. (Pp. 364 + Index ; illustrated. $10.00.) Washington: Psychodynamics Monograph Series. 1959.

From 1949 to 1953 Dr. Karpman arranged for a symposium on juvenile delinquency to be held each year at the Annual Meeting of the American Orthopsychiatric Association. The proceedings, previously reported with some curtailment in the journal of the Association, are now collected and published in full. They make a large and wordy book, profusely illustrated with very crude drawings, which faithfully reflects the mixture of confidence and ignorance that unfortunately still characterizes the approach by child psychiatrists to the alarming problems of juvenile delinquency. The extent to which psychopathic personality can be held responsible for children's misconduct is a recurring theme in the book: the discussions of it throw disconcerting light on the possible outcome of those compulsory measures for dealing with psychopathic adolescents which the new Mental Health Act now provides in Great Britain.

Hysterie, Reflex und Instinkt, 6th ed. By Ernst Kretschmer. (Pp. viii + 148, DM 12.80.) Stuttgart: Georg Thieme. 1958.

The last edition of this book appeared in 1947. Little has been learnt about hysteria in the intervening years, and the changes in this latest edition are correspondingly few. A case history is introduced to illustrate what the author calls a "cascade effect" in which the stimulus of an emotional shock spreads outward and releases a series of severe changes of a somatic as well as a psychological nature. Imu, a condition probably identical with Latah, is described; and a short note added on the way the vegetative nervous system is affected by that voluntary increase in reflex responses which Kretschmer postulates in hysteria. The book exemplifies the curiously indeterminate nature of clinical conceptions of hysteria and its psychopathology.

Stuttering: A Psychodynamic Approach to Its Understanding and Treatment. By Dominick A. Barbara. (Pp. 255. 25*s*.) London: Hutchinson. 1958.

Dr. Barbara, who is himself a stutterer, is a devoted adherent of the psychoanalytic theory and practice developed by the late Dr. Karen Horney. His book is a sustained explanation of stuttering in terms of Dr. Horney's theory of neurosis. His considerable experience of treating this irksome handicap is not turned to full account, as only one chapter, out of the 17 that make up the book, is concerned directly with treatment, and the author here absolves himself from detailed description of methods. He does not give any data enabling the reader to judge the success of treatment carried out along the broad lines he advocates, and all in all his book is disappointingly vague.

Communication, Organization and Science. By Jerome Rothenstein; Foreword by C. A. Muses. (Pp. xcvi + 110. $3.50). Indian Hills, Colorado: The Falcon's Wing Press. 1958.

This is a book for physicists interested in cybernetics and the theory of communication. Philosophical, psychological, and linguistic questions are discussed in a speculative way, and particular attention paid to the concept of entropy. Two-fifths of the book is taken up with an obscurely written foreword by Dr. Muses.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books received.)

A Short History of Psychiatry [translated from the German by Sulammith Wolff]. By Erwin H. Ackerknecht. (Pp. xi + 98; 9 photographs. 25*s*.) London: Hafner Publishing Co. 1959.

Va Prospectus **Research in Aging.** Veterans Administration 1959. (Pp. v + 125; 48 figures. $1.50.) Washington: U.S. Government Printing Office. 1959.

The Pathology of Tumours of the Nervous System. By Dorothy S. Russell and L. J. Rubinstein, with a chapter on "Tissue Culture in Relation to Tumours of the Nervous System" by C. E. Lumsden. (Pp. iii + 318; 286 figures. 70*s*.) London: Edward Arnold. 1959.

Anatomy of the Human Body. By R. D. Lockhart, G. F. Hamilton, and F. W. Fyfe. (Pp. ix + 697; 965 figures. 105*s*.) London: Faber and Faber. 1959.

A Textbook of Neurology, 2nd edition revised. By H. Houston Merritt. (Pp. 765; 182 figures + 123 tables. 93*s*. 6*d*.) London: Henry Kimpton. 1959.

Enjoy Work and Get Fun Out of Life. By O. A. Battista. (Pp. xxi + 229. 7*s*. 6*d*.) Kingswood, Surrey: Elliot Right Way Books. 1959.

Klinik und Therapie Symptomatischer Anfallsleiden. By K. Nittner and H. W. Steinmann, and **EEG und Hirntrauma.** By H. W. Steinmann; Foreword by Prof. Dr. W. Tonnis. (Pp. viii + 175; 68 figures. DM 36.80.) Stuttgart: Georg Thieme. 1959.

The Degenerative Back and Its Differential Diagnosis. By P. R. M. J. Hanraets. (Pp. xi + 690; 315 figures, 12 in colour. 105*s*.) London: D. Van Nostrand. 1959.

Family and Class Dynamics in Mental Illness. By Jerome K. Meyers and Bertram H. Roberts. (Pp. xi + 295. 56*s*.) London: Chapman and Hall; New York: John Wiley. 1959.

Sympathectomy. An Anatomical and Physiological Study with Clinical Applications. By P. A. G. Monro. (Pp. xx + 290; 84 figures. 75*s*.) London: Oxford University Press. 1959.

Obnubilations Comas et Stupeurs: Etudes Electro-encéphalographiques. By H. Fischgold and P. Mathis. (Pp. 126; 54 figures. Fr. Fr. 3,000.-.) Paris: Masson. 1959.

Cliniques Radiologiques, 1st series: L'Agrandissement radiographique direct dans l'examen de la base du crane et des microsfractures du rocher. By J. Roussel, in collaboration with P. Schoumacher, M. Pernot, and R. Poiré; Foreword by Prof. P. Larmarque. (Pp. 102; 59 figures. Fr. frs. 3,200.-.) Paris: Masson et Cie. 1959.

Neuro-Ophtalmologie, Vols. I and II. By L. Guillaumat, P.-V. Morox, and G. Offret; Foreword by Prof. Th. Alajouanine and Prof. D. Petit-Dutaillis. (Pp. 1388; 464 figures, 11 colour plates. Fr. frs. 21,500.-.) Paris: Masson et Cie. 1957.

Psychiatrische und Nervenklinik. By Kurt Kolle. (Pp. xvi + 252. DM 19.80.) Stuttgart: Georg Thieme. 1959.

The Postnatal Development of the Human Cerebral Cortex, Vol. VI: *The Cortex of the Twenty-Four-Month Infant.* By J. LeRoy Conel. (Pp. 309; 201 figures. 100*s.*) Harvard University Press (London: Oxford University Press). 1959.

The Historical Development of Physiological Thought. [A Symposium held at The State University of New York Downstate Medical Center]. Edited by Chandler McC. Brooke and Paul F. Cranefield. (Pp. xiii + 401. 45*s.*) London: Hafner Publishing Co. 1959.

Insulin Treatment in Psychiatry. Edited by Max Rinkel and Harold E. Himwich. (Pp. xxxiii + 386; illustrated. $5.00.) New York: Philosophical Library. 1959.

The Barbiturate Withdrawal Syndrome. A Clinical and Electroencephalographic Study. By Munke Hertel Wulff. (Pp. 173; 19 figures. D.kr. 28.-.) Copenhagen: Ejnar Munksgaard. 1959.

Right-Left Discrimination and Finger Localization, Development and Pathology. By Arthur L. Benton; Foreword by Adolph L. Sahs. (Pp. xv + 185. $7.00.) New York: Paul B. Hoeber. 1959.

"Allergic" Encephalomyelitis [Proceedings of a Symposium on Experimental "Allergic" Encephalomyelitis and Its Relation to Other Diseases of Man and Animals]. Edited by Marian W. Kies and Ellsworth C. Alvord, Jr. (Pp. xiv + 576; illustrated. £5 2*s.* 6*d.*) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1959.

Anastomoses Between the Leptomeningeal Arteries of the Brain. Their Morphological, Pathological and Clinical Significance. By Henri M. Vander Eecke; Preface by Raymond D. Adams. (Pp. xvi + 160; 62 figures. 57*s.* 6*d.*) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1959.

Heavy Metals and the Brain. By John N. Cumings. (Pp. vii + 161. 32*s.* 6*d.*) Oxford: Blackwell Scientific Publications. 1959.

Trigeminal Neuralgia: Its History and Treatment. By Byron Stookey and Joseph Ransohoff. (Pp. xv + 366; 86 figures. 81*s.*) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1959.

A Manual of Psychiatry. By K. R. Stallworthy. (Pp. 365. N.Z. price 30*s.*) Christchurch, New Zealand: N. M. Peryer. 1959.

Allgemeine Neurosenlehre auf Psychoanalytischer Grundlage, 2: *Neubearbeitete und er Weiterte.* By Hermann Nunberg; Foreword by Sigmund Freud. (Pp. 435. DM 38.-.) Berne and Stuttgart: Verlag Hans Huber. 1959.

Pain. Problems Pertaining to the Transmission of Nerve Impulses which Give Rise to Pain. By W. Noordenbos. (Pp. 182; 40 figures. 42*s.* 6*d.*) London: D. Van Nostrand. 1959.

Schizophrenia: An Integrated Approach [Papers presented at the Symposium of the Hawaiian Divisional Meeting of the American Psychiatric Association, 1958]. By Alfred Auerbach. (Pp. viii + 224. $5.50.) New York: The Ronald Press. 1959.

The Cranial Nerves. Anatomy and anatomico-clinical correlations. By Alf Brodal. (Pp. 144; 25 figures. 15*s.*) Oxford: Blackwell Scientific Publications. 1959.

Surgery in World War II: Neurosurgery, Vol 1. Prepared and published under the direction of Major General S. B. Hays; Editors for **Neurosurgery** R. Glen Spurling and Barnes Woodhall, with the assistance of Elizabeth M. McFetridge. (Pp. xix + 466; 130 figures. $5.00.) Washington, D.C.: Walter Reed Army Medical Center. 1958.

Die Entfremdungserlebnisse. By Joachim-Ernst Meyer. (Pp. viii + 64. DM 12.60.) Stuttgart: Georg Thieme. 1959.

Diagnostic des Lésions Intra-Craniennes par les Radio-Isotopes (Gamma-encéphalographie). By Thérèse Planiol; Foreword by Prof. D. Petit-Dutaillis. (Pp. 258; 153 figures. Fr. fr. 5,000.-.) Paris: Masson. 1959.

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